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14. ABSTRACT: The overall goal of this project remains to bring epigenetic therapy strategies to have major impact for the management of advanced ovarian cancer (OC). This past year, we continue to make exciting advances and all of our pre-clinical work is about to impact a leveraged clinical trial now ready to start wherein low dose therapy targeting DNA demethylation will be paired with immune checkpoint therapy. Our latest studies of a mouse model of serous ovarian cancer has progressed significantly in which we have identified the demethylating agent, 5-aza-cytidine (AZA) potently stimulates tumor immune attraction of T-cells to the tumor microenvironment. This augmented by addition of a histone deactylase inhibitor (HDACi) in a newly derived regimen – and addition of the immune checkpoint therapy, anti-PD1 adds to tumor inhibition and prolongs survival of the mice. We are now working to determine whether an AZA induced interferon triggering pathway involving upregulation of a cytosolic double stranded RNA(dsRNA) sensing system and of endogenous retroviral transcripts (ERV's), published last year, is the mechanism triggering the above immune response.

15. SUBJECT TERMS – key words or phrases identifying major concepts Epigenetic therapy, advanced ovarian cancer, DNA demethylation, histone deactylases, immune checkpoint therapy, viral defense, immune cell attraction

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Table of Contents

	Page
1. Introduction…….	4
2. Keywords…….	4
3. Accomplishments……..……...	4
4. Impact……...……	11
5. Changes/Problems...…..……	12
6. Products……..……..…..…….	13
7. Participants & Other Collaborating Organizations…….	13
8. Special Reporting Requirements……	52
9. Appendices……	53

1. INTRODUCTION

The goal of our project remains to develop eventual "epigenetic" therapy strategies, with relatively low toxicities, which can potentially robustly extend the life expectancy of women with advanced ovarian cancer (OC). This has been an exciting year of progress for this goal as we pursue strategies which take advantage of the potential for epigenetic therapy to normalize multiple pathways which are abnormal in cancer initiation and/or progression. We continue moving forward in bringing our concepts fully to bear on the treatment of OC. This past year, we have continued to concentrate on **Specific Aim 3:** *to study how epigenetic therapy may sensitize OC cells to subsequent immunotherapies which targets checkpoints which are driving immune tolerance*. As during the previous year, our group of research leaders including Cindy Zahnow, Dennis Slamon, Drew Pardoll, and Peter Jones and a final year of work from our first mentored trainee for our project, Kate Chiappinelli, made exciting progress for **Major Task 1**: *to develop the in-vitro pre-clinical systems to outline the sensitivities and derive molecular signatures that track with these,* and **Major Task 2:** *to develop in-vivo pre-clinical systems to outline the potential efficacy of epigenetic therapy sensitization to immunotherapy for targeting checkpoints which drive immune tolerance*. This progress is all occurring in the setting of a leveraged clinical trial, headed by Dennis Slamon, which is now about to start for advanced serous OC and which pursues this above potential for epigenetic therapy to improve the efficacy of immune checkpoint therapy. We also continue to use our findings to develop biomarker strategies, to be investigated in the above leveraged trial, which can potentially predict patient responses and monitoring of therapy. Other key progress aspects will also be outlined. We have also focused, and made important progress in on **Specific Aim 4:** *Develop new combinations of epigenetic drugs which may provide for the highest level of efficacy for management of OC and* **:** **Major Task 1:** *Follow biochemical hypotheses for designing combinations of the epigenetic drugs used in all studies above with new agents targeting additional steps in chromatin control of gene expression – the goal is to improve reversal of abnormal gene silencing in OC.*

2. KEYWORDS

1) epigenetic therapy; 2) DNA demethylation; 3) histone deacetylases; 4) immune evasion; 5) immune checkpoint therapy; 6) immune attraction.

3. ACCOMPLISHMENTS

What were the major goals and objectives of the project?

The overall goals remain identical to those outlined in the original proposal. This past year, as introduced earlier, we have concentrated particularly on:

A. Specific Aim 3: *to study how epigenetic therapy may sensitize OC cells to subsequent immunotherapies which targets checkpoints which are driving immune tolerance*. We have, with participants of key leaders, Cindy Zahnow, Dennis Slamon, and Drew Pardoll, with much lead work from the mentored postdoctoral fellow for our project, Kate Chiappinelli, made exciting progress for **Major Task 1**: *to develop the in-vitro pre-clinical systems to outline the sensitivities and derive molecular signatures that track with these,* and **Major Task 2:** *to develop in-vivo pre-clinical systems to outline the potential efficacy of epigenetic therapy sensitization to immunotherapy for targeting checkpoints which drive immune tolerance*. The major findings, as detailed directly below, involve discoveries providing key insight into how epigenetic therapy may help reverse immune evasion to help sensitize to immune checkpoint therapy for OC, and a biomarker system for potentially predicting patient responses and monitoring therapy.

***What was accomplished under these goals*?**

A. Specific Aim 3: Major Task 1: *to develop the in-vitro pre-clinical systems to outline the sensitivities and derive molecular signatures that track with these.* Progress is as follows:

1. *As mentioned last year, we completed a body of work, for which our mentored trainee, Kate Chiappinelli, was the first author on a Cell paper (Chiappinelli et al, Cell, 2015).* In this, we defined that, in human OC cells, a cytosolic double stranded RNA (dsRNA) viral defense pathway is a core functional circuit for an AZA induced interferon response and we defined the potential for constituent genes and endogenous retroviral transcripts (HERV's) in this drug response for predicting responses to immune checkpoint therapy (**Fig. 1**). Central to this induction is upregulation of a viral defense pathway. These data are now fueling work in specific aims later below for understanding, in a mouse OC model, the functionality of this pathway for driving tumor induced, immune cell attraction, for deriving key biomarker strategies, and for developing new epigenetic therapy approaches for OC.

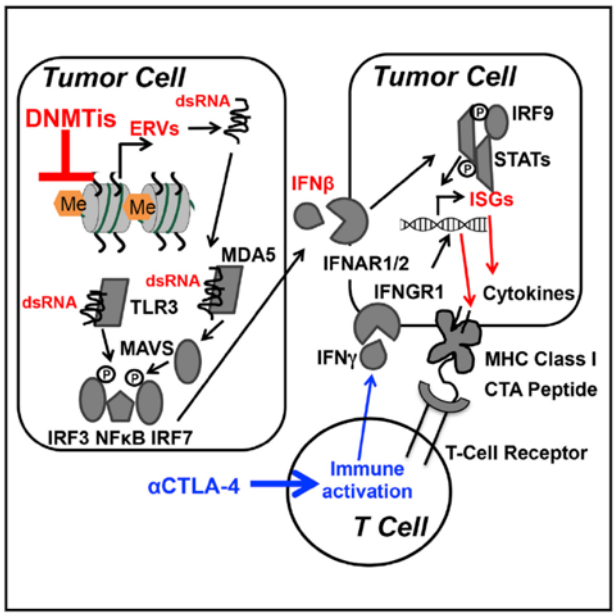


Fig. 1. DNA methyltransferase inhibitors (DNMTis) inhibit DNA methylation of LTR's for endogenous retroviruses (ERVs) to upregulate their transcription in OC tumor cells to induce a growth-inhibiting immune response. High expression of the genes associated with the anti-viral response have the potential to sensitize to immune checkpoint therapy which blocks ligand mediation of immune tolerance including CTLA-4 and PD-L1.

B. Specific Aim 3: Major Task 2: *to develop in-vivo pre-clinical systems to outline the potential efficacy of epigenetic therapy sensitization to immunotherapy for targeting checkpoints which drive immune tolerance*. We are making great progress in this task with Cindy Zahnow continuing to take the lead with the collaborations previously defined. Specific accomplishments are:

1. *We have now fully implemented the syngeneic mouse model described in our last progress report to study, in-vitro and in-vivo the potential efficacy of epigenetic therapy sensitization to immunotherapy for targeting checkpoints which drive immune tolerance.* Again, the work has involved great participation from our mentored post-doctoral fellow, Dr. Chiappinelli and a graduate student, Meredith Stone. The model is the MOSE mouse model of serous OC and we have kept pace with the goal to complete much of this task by the end of year two with a paper now in full preparation. In this model, as we have previously outlined, the mice receive tumor cells intraperitoneally and develop ascites in a manner similar to what can occur in patients with advanced OC. This model is known to be poorly immunogenic giving us the opportunity to determine whether our epigenetic therapy strategies can alter this scenario and sensitize to immune checkpoint therapy in so doing. The following important data have emerged:

a. AZA treatment of MOSE cells leads to up-regulation of viral defense genes, ERV's, antigens and key cytokines: We showed last year that there is good conservation between human and mouse tumor cells for viral defense genes induced by AZA which we propose have a major role in our scenario for sensitizing to immune checkpoint therapy. We have now extended these data to show how longer periods of AZA treatment progressively accomplish not only these increases, but also those for ERV's, key antigens, and key immune attracting cytokines (**Fig. 2**). All of these factors potentially contribute to how epigenetic therapy may enhance the efficacy of immune checkpoint therapy. In

addition, we have shown that unlike in human OC cells, adding a histone deactyase inhibitor (HDACi) (more details on these later below) to AZA does not augment the AZA effect (**Fig. 2D**).

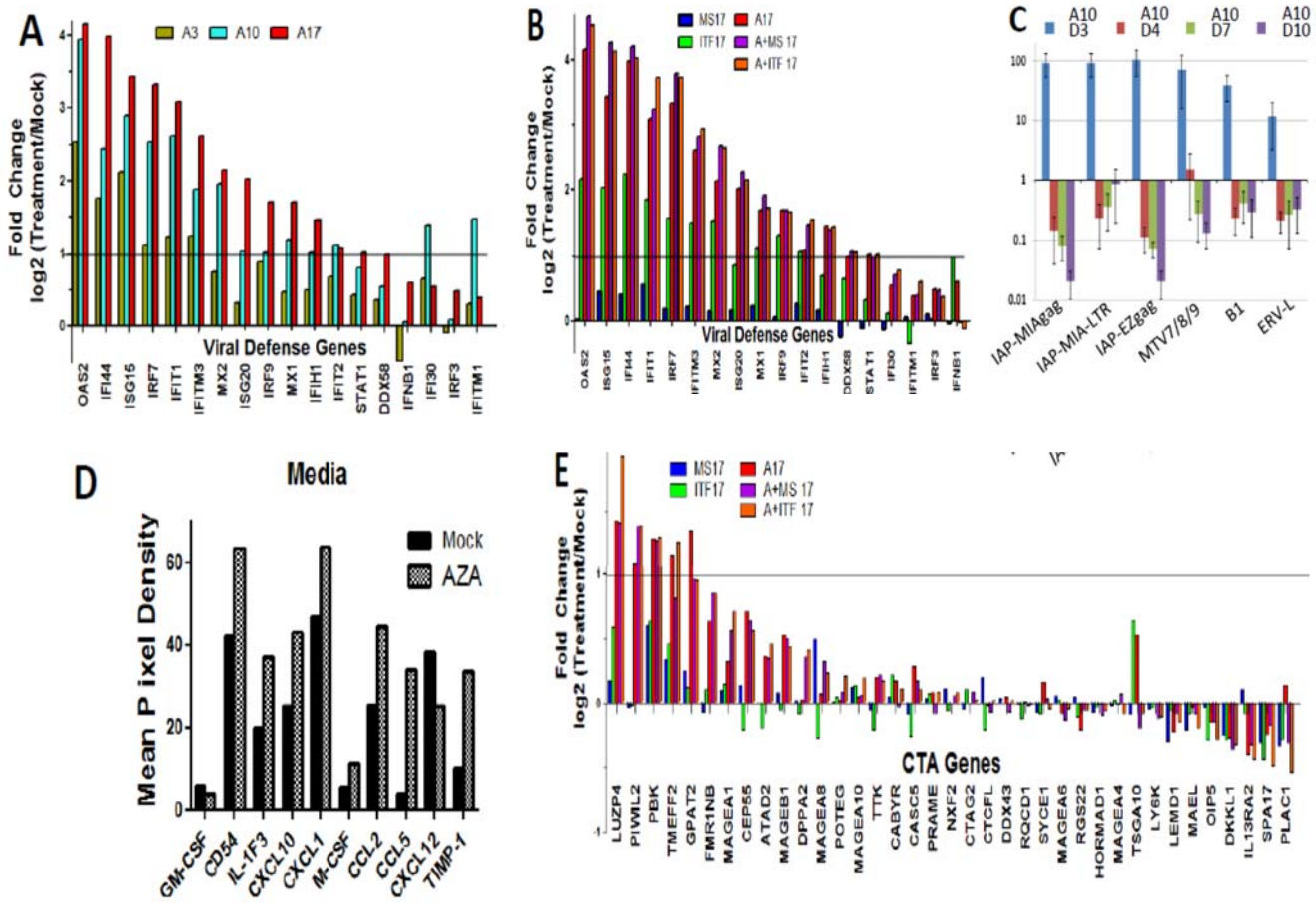


Fig. 2. The effects of different AZA(500 nM) with and without HDAC inhibitors (HDACi's)(100 nM) and treatment times on the up-regulation of viral defense genes, ERV's, antigens and cytokines in the MOSE OC cells. Panel A – the effects of AZA alone on viral defense genes: Y-axis = log fold change over mock treatment; X-axis = the viral defense genes tested. The number of treatment days is shown at the top. Panel B – The effects of adding HDACi's to AZA on viral defense genes: the HDACi's are MS = entinostat or MS275 from Syndax, and ITF from Italico-Phramacia. The X and Y axis and times at the top are as in A. Panel C – The effects of adding HDACi's to AZA on mouse ERV's: These show a fast increase and then downregulation following treatments. The X and Y axis and times at the top are as in A. Panel D – upregulation of key, immune attracting cytokines by AZA in MOSE cells. Panel E – the effects of AZA and AZA + the HDACi's on cancer testis antigens (CTA) in MOSE cells.

b. MOSE OC cells pre-treated with AZA and placed into mice increases the recruitment of immune cells into ascites fluid (**Fig. 3**). We have extended, markedly, results reported last year for how in-vitro exposure of MOSE cells with 500 nM AZA treatment for 10 days, followed by injecting the cells into the abdomen of mice leads to marked delay of ascites development (**Fig. 3 – top left panel)**. We have added to this, now more major immune cell subtypes and the effects of adding HDACi's to AZA. These alone cannot stimulate recruitment of the cells but augment the effects of AZA. These results document that a key part of AZA effects involve inducing, directly in tumor cells, signals which foster recruitment of multiple, lymphocyte and other immune cell subsets to the tumor microevironment and suppression of macrophages.

c. Developing the above mouse model for in-vivo treatment employing epigenetic therapy to sensitize to immune checkpoint therapy. This is the most important aspect of our mouse work, and

again has been expanded significantly since the last progress report. In so doing, we continue to be far ahead of the predicted development of this from year 2 to 4.

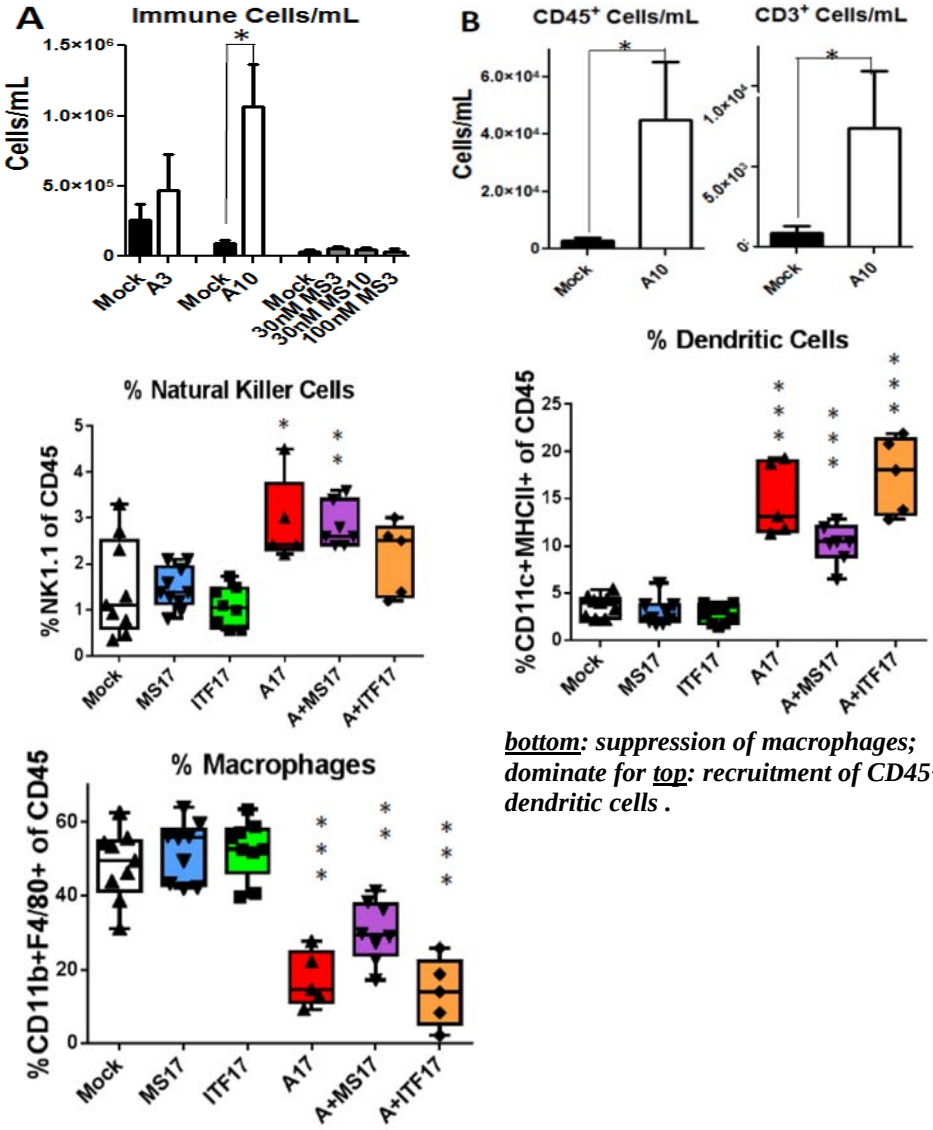


Fig. 3. The effects of ex-vivo AZA (500 nM) treatment of MOSE cells, with and without HDACi') (100 nM), on the ability of the tumor cells to attract immune cell subsets to ascites (cells /ml when injected into immune competent mice. For HDACi's, MS = entinostat from Syndax and ITF = givinostat from Italico-pharmacia. A = AZA. No.'s after each drug = days of exposure. <u>Note in</u> <u>Panel A</u>: <u>top</u>: AZA effects dominate for inducing total immune cells/ml of ascites fluid at days 3 and 10, and no effects of MS alone; <u>middle:</u> effects on up-regualtion of CD45+ and CD3+ cells; <u>bottom</u>: suppression of macrophages; <u>Note in</u> <u>Panel A</u>: AZA effects dominate for <u>top</u>: recruitment of CD45+ and CD3+ cells and <u>bottom</u>, dendritic cells .

For these studies, as introduced last year, we have developed a treatment regimen wherein low doses of AZA with and without low doses of HDACi's are administered chronically for weeks at a time. Mice tolerate these doses extremely well and this is a strategy that holds great promise for evolving into future clinical trials. This regimen is especially different in terms of addition of the HDACis which previously are usually given at higher doses and only intermittently. Our hypothesis is that our combined regimen employing the low dose chronic HDACis will be tolerable and provide a more chronic pressure on chromatin to enhance the viral defense gene and ERV up-regulation which may be key for sensitization to immune checkpoint therapy. We have pursued this hypothesis by adding anti-PD1 treatment to the developed dosing regimen. The choice and use of the HDACi's has been made based our intensive studies of multiple such drugs with a focus on the HDAC family members which we want to target for gene up-regulation, nuclear HDAC's 1 and 2. We have then focused, as noted in earlier studies outlined in previous sections above, on the HDACi's, entinostat (MS275) givinostat (ITF). The former has an excellent Ki against HDAC1, while the latter is even better for HDAC1 and also targets HDAC2. Our results to date are as follows:

1) <u>*Treatment model*</u>. The schema used for all the in vivo studies below sections below is shown in Fig**. 4A**.

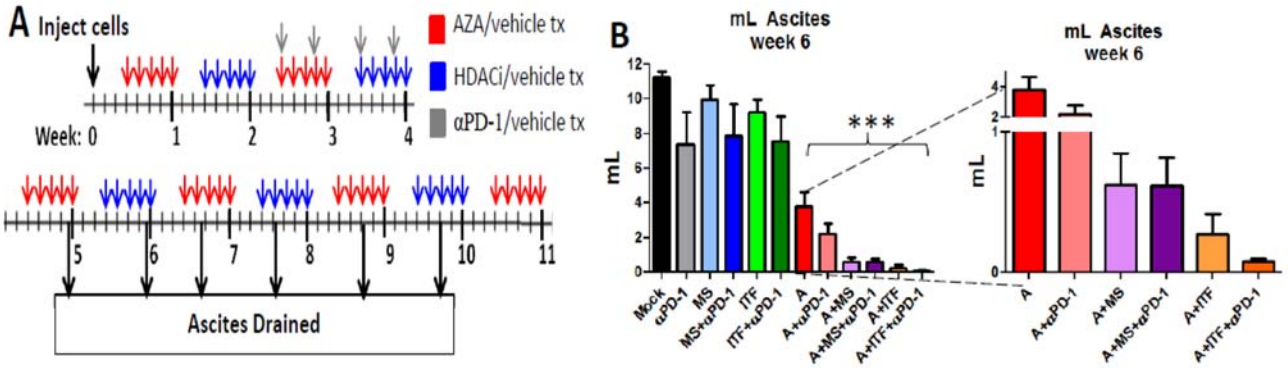


Fig. 4. A. Treatment schema with AZA given each day at 0.5mg/kg and the HDACi's at 0.2 mg/kg with and without anti-PD1. B. Ascites accumulation at 6 weeks. Note the marked blunting with AZA (A) alone and AZA plus especially the HDACi's (ITF and MS) and especially with all 3 drugs.

2) *Ascites is best reduced with AZA combined with anti-PD-1 and HDAC inhibitors (**Fig. 4B**)*. AZA alone is capable of suppressing accumulation of ascites in the MOSE model and its combination with HDACi's and especially with all three drugs together blunts this most severely.

4) *In vivo AZA treatment combined with anti-PD-1 and/or HDACi's increases ascites accumulation of multiple immune cell subsets, including activated (IFNγ+) CD8 T cells (**Fig. 5B**) and decreases macrophages. inhibitors increases CD3+ T cells in the tumor environment, and increases. The increased activation of T cells is specific to AZA and/or plus HDACi and anti-PD-1 (**Fig. 5**)*. In these studies we have learned that AZA alone, and further when combined with HDACi's and with immune checkpoint anti-PD1 can recruit immune subset cells which would attack tumor cells (CD8 T-cells and NK cells) and suppress total macrophages which are often tumor activating. This drug, but also the HDACi, entinostat (MS in **Fig. 5**) can decease a population of white cells (MDSC's) which can suppress tumor cell immunity mediated by CD8 cells.

5) *In vivo AZA combined with MS275 or ITF, and/or anti-PD-1 significantly increases survival in mice (**Fig. 6**)*. Most importantly relative to all of the data shown in Figs 3-5, the epigenetic therapy with AZA and HDACi's, plus addition of anti-P1 immune therapy can prolong the survival of mice implanted with MOSE OC cells. We believe this can be optimized even further by more treatment with this latter therapy in our model which in all of our studies to date has been limited to the four doses shown in **Fig. 4A**. These data are extremely important to the leveraged clinical trial with AZA which, under Dennis Slamon's as noted earlier, is now ready to begin – and to use of the viral defense genes and ERV's as markers which may predict, and help monoitor, any efficacy seen in this trial.

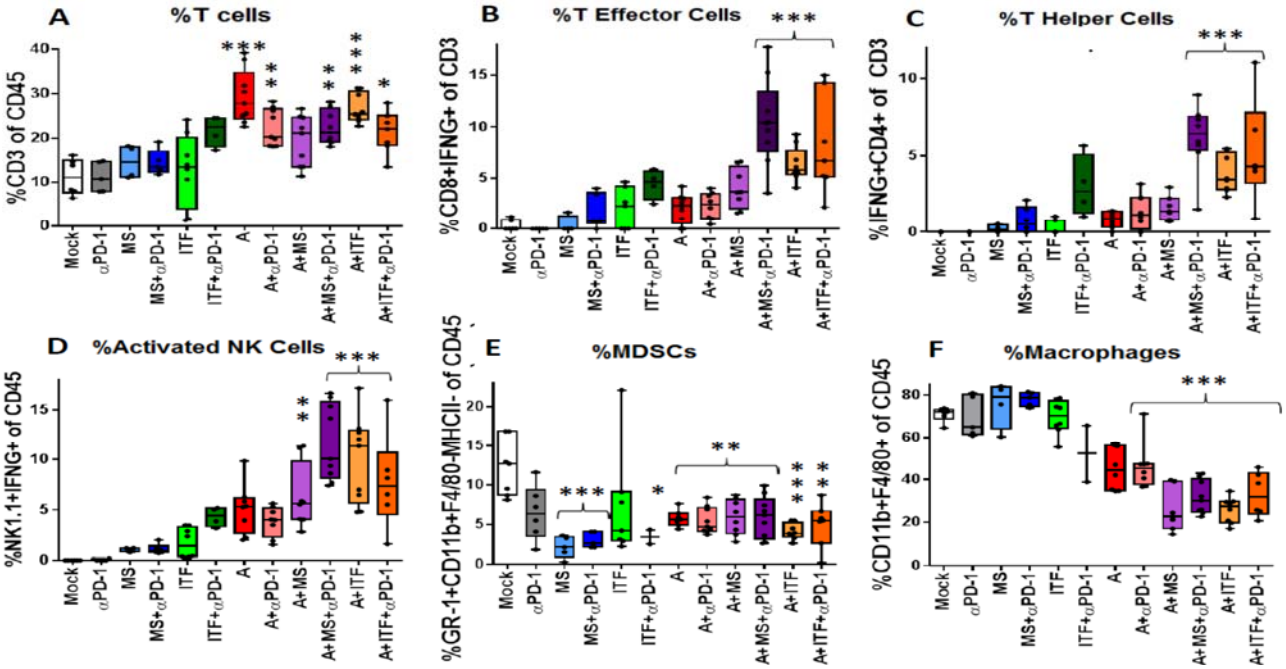


Fig. 5. Effects of in-vivo treatment with the schema in Fig. 4A of AZA and/or entinostat (MS) and/or givinostat (ITF) on accumulation in ascites of % T-cells of total T-cells (A), % activated CD8 T-cells with interferon gamma (B), %T-helper cells (C)) and %activated NK cells (D). The HDACi, MS with and without the other drugs, and AZA without and with the other drugs suppress % immune tolerance inducing macrophage-myelocyte (MDSC's) cells (E) and AZA plus the other drugs suppresses % overall macrophages (F).

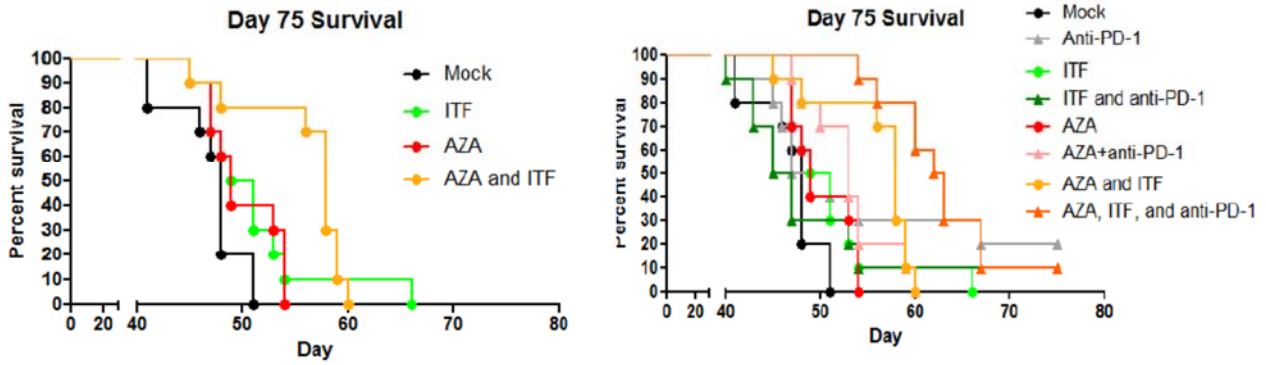
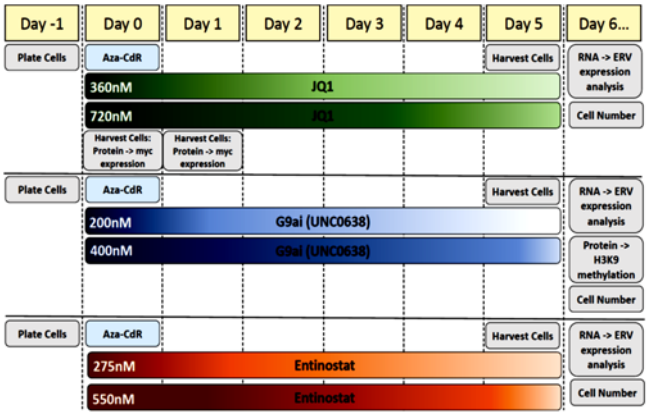


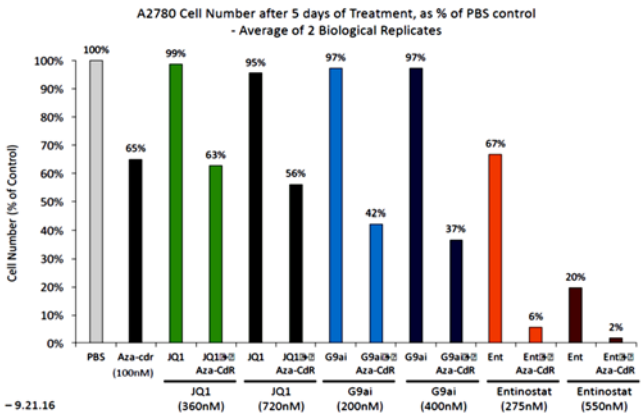
Fig. 6. Effects of in-vivo treatment with the schema in Fig. 4A of AZA and/or entinostat (MS275) and givinostat (ITF) on survival of the mice (left panel) and with the addition of anti-PD-1 treatement (right panel). The colr codes for the teratments is shown to the right in the right panel. Sacrifice is always based on mouse discomfort from ascites accumulation. Note that AZA + the HDACi, ITF (orange line), significantly improves survival over the other drugs alone (left panel). Note that the addition of anti-PD-1 to AZA + ITF (dark orange line), provides even further survival advantage (right panel).

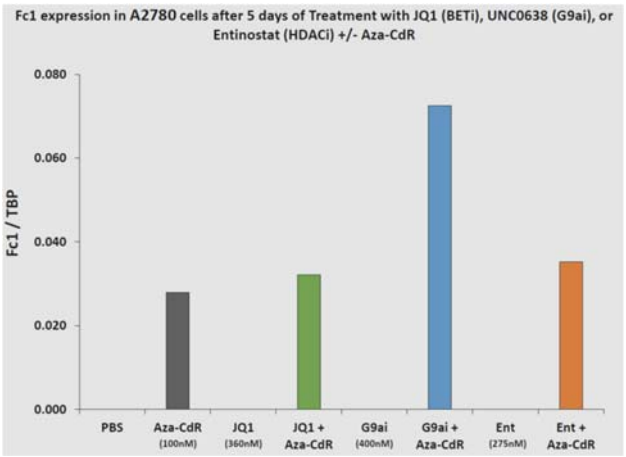
C. Summary of progress for Specific Aim 3 and majors tasks 1 and 2: As outlined in the sections above, our progress has been extensive in the past year in further understanding how use of epigenetic drugs which inhibit DNA methylation (AZA) and inhibit histone deactylases (HDACi) may be used to increase the efficacy of immune checkpoint therapy in patients with OC. Our new strategy to augment the effects of AZA alone by combining this drug with a deeply researched plan for chronic administration of low dose HDACi's has now been extensively explored over the past years as outlined in Figs. 2-6. Importantly, this includes fully taking this therapy strategy to in vivo treatment to our mouse MOSE OC model and in combination with immune checkpoint therapy. All of this now shows that the combined epigenetic therapies increase tumor signaling for attraction of activated T-cells and provide for anti-tumor effects with prolongation of survival. These data provide substrate

for our honing this treatment regimen further during the next year, and we will now stress formally investigating whether the drug induced up-regulation of viral defense genes and the ERV's is, indeed a major stimulus for the host immune cell attraction to ascites in our model. We will continue to explore the implications of all of these studies towards the leveraged clinical trial about to start for patients with advanced OC.

D. Specific Aim 4: *Develop new combinations of epigenetic drugs which may provide for the highest level of efficacy for management of OC*: **Major Task 1:** *Follow biochemical hypotheses for designing combinations of the epigenetic drugs used in all studies above with new agents targeting additional steps in chromatin control of gene expression – the goal is to improve reversal of abnormal gene silencing in OC*: These studies, under the direction of Dr. Peter Jones at the Van andel Research Institute (VARI), with close collaboration from Dr. Baylin has made some important progress during the past year. Last year, we reported early results that the potent inhibitor of oncogenic C-MYC function, JQ1 may augment AZA for induction of genes. We have continued these studies but, among new paradigms investigated to date, the most potent effects occur with addition of a drug (UNC0638) specifically blocking the histone methyltransferase, G9A. This enzyme adds the transcriptionally repressive mark, histone 3, lysine 9, di methyl (H3K9me2) to chromatin. G9A interacts with the major enzyme which maintains abnormal DNA methylation in cancer , DNMT1 – and the Baylin lab has shown in the past that this enzyme, and the H3K9me2 mark is tightly tied to the start sites of genes affected by abnormal DNA methylation in cancer. This mark, and G9A, leave these genes when the abnormal methylation is reversed by AZA, the key drug being used in our studies of OC in the previous sections and in the leveraged clinical trial to start shortly. We are now finding that UNC0638 augments Aza reduced cell growth and increased ERV/viral-defense gene expression in A2780, human OC cells (**Fig. 7**). This new drug alone did not affect cell growth or ERV/viral-response gene expression. The HDACi, entinostat usually remains the most effective drug in combination with AZA for reducing cell growth and increasing expression of two of three HERV's so far tested but UNC0638 can sometimes be better for augmenting expression (**Fig. 7** – lower two panels).







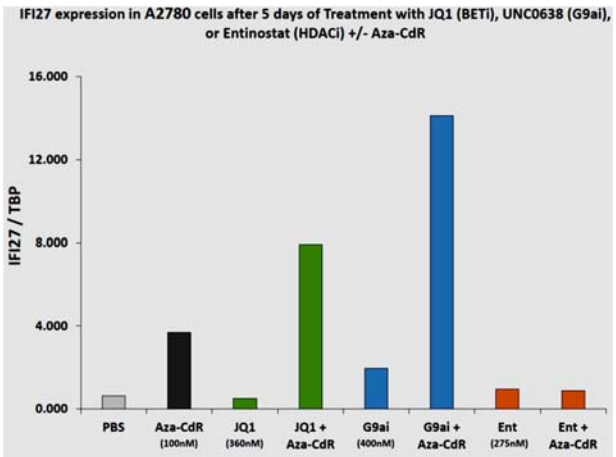


Fig. 7. Effects of in-vitro treatment with the schemas shown (top tight panel) of deoxy-aza-cytidine (5-aza-CdR), entinostat, JQ1, and UNC0638 (G9ai). Note the enhanced growth inhibition (Y-axis) over AZA with G9a1 and with entinostat. (top right panel). Bottom two panels show augmentation of expression (ratio over a control gene, TBP – Y-axis) for a frequently AZA activated ERV, Fc1 (left) and of a key viral defense genes, IFI27 (right – note for this gene in these cells, than AZA + Ent).

We will be building heavily on these results during the coming year and looking at additional important drugs.

What opportunities for training and professional development did the project provide?

The first two years year of this grant have been exceptionally important in this regard. Dr. Chiappinelli, our mentored fellow trainee, has benefitted enormously from participation in all of the work outlined in the above sections and the work and become a real leader in these multiple projects. Her academic growth, is discussed in detail in Section 8, Special Reporting, later below.

A graduate student, Meredith Stone, has also benefitted tremendously from principally working with TEAL faculty investigator, Cindy Zahnow on the MOSE mouse model and is the first author on a paper now scheduled for submission within the next month.

How were the results disseminated to communities of interest?

As outlined in multiple sections below, key studies during the first year were published in Cell (Chiappinelli et al, 2015) and have been presented in several research forums for OC research including an AACR sub-meeting on OC and the general AACR meeting. In addition, Dr. Chiappinelli's work has been specifically reviewed by request from our group (Chiappinelli et al, Cancer research, 2016) and also as an editorial in the New England Journal of Medicine (Dear AE. Epigenetic Modulators and the New Immunotherapies. NEJM 374(7):684-6, 2016). In addition, the recent Cell paper (included in Appendix), described in the Progress Report above, has generated great interest in our work and its implications for the therapy of OC.

What do you plan to do during the next reporting period to accomplish the goals and objectives?

During the next year we are hopeful to continue the same pace and volume of work as during this past one. We are generating a manuscript on the data in Figs. 5-10 which we hope to submit by the end of 2016 and we will continue attending the many meetings which are highlighted in the sections below.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

The work in the past year continues to have much impact for understanding and treating OC, and specifically for the potential for epigenetic therapy to increase the efficacy of immune checkpoint therapy and for providing insight into the mechanisms that may be involved. As per sections above, the trainees and faculty involved with the TEAL have been called upon for many lectures at OC specialty meetings and general cancer research meetings. The molecular studies, especially those in the recent Cell paper, have provided the nidus for the correlative science studies in the upcoming trial with Celgene and Merck to test whether AZA therapy can sensitize to anti-PD1 therapy for patients with advanced OC. This will involve using expression of the viral defense gene panel and ERV's to determine whether this predicts and tracks with therapy efficacy.

***What was the impact on other disciplines*?**

Our studies of OC outlined in this second year Progress Report continue to extend the implications of our studies for cancer in general. The AZA induced viral defense signature and ERV up-regulation can be seen for colon cancer and NSCLC and gene expression subgroups for potential predictive value are observed in breast, colon, melanoma, NSCLC as well as OC in TCGA data as reported in our recent Cell paper. In addition to the relevance for cancer, the studies outlined in Figs. 3-6 particularly extend what we have to teach about immunology as it pertains to cancer.

***What was the impact on technology transfer*?**

The entire AIM signature, inclusive of the viral defense gene signature and ERV transcripts are the subject of a patent applied for concerning their use as biomarker systems to predict and monitor the efficacy of applying epigenetic therapy to sensitize patients with advanced OC, and all cancer types, to immune checkpoint therapy. Several companies have approached Hopkins about the potential to license this biomarker signature.

***What was the impact on society beyond science and technology*?**

Hopefully the biggest impact of our studies will be for patients. As mentioned in the progress report, a trial for testing our paradigm for sensitizing to immune checkpoint therapy in patients with advanced OC is scheduled to start in the next month or two. Hopefully, efficacies observed in this trial will provide the greatest impact we could seek for our work.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

At present, we do not anticipate any major changes to our work scope and directions. We have continued to focus on Specific Aims 3 and 4, as focused upon in this progress report. All of these studies are aimed at trying to maximize our epigenetic therapies for OC and adapting our mouse OC model for employing optimal timing and dosage for the combination of AZA plus the HDACis, entinostat and givinostat plus anti-PD-1. We are now going to stress formally investigating the direct role of our viral defense pathway and ERV's for the efficacies of our approaches in this model. We will also continue work in Specific Aims 1 to test the direct anti-tumor effects, alone, of our combinatorial epigenetic therapy with AZA plus HDACis on OC in the in-vitro and in-vivo systems we are evolving. We will also pursue the ongoing work with new drug combinations in Specific Aim 4. This includes deciphering mechanisms and pathways involved with any efficacies seen.

Actual or anticipated problems or delays and actions or plans to resolve them

None anticipated at this time.

Changes that had a significant impact on expenditures

None anticipated at this time.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

None anticipated at this time.

6. PRODUCTS

Publications, conference papers and presentations

Publications

Chiappinelli KB, Zahnow CA, Ahuja N, Baylin SB. Combining Epigenetic and Immunotherapy to Combat Cancer. Cancer Res. 2016 Apr 1;76(7):1683-9. doi: 10.1158/0008-5472.CAN-15-2125. Epub 2016 Mar 17. PMCID: 4873370. (a review - no acknowledgements allowed by journal)

Strick R, Strissel PL, Baylin SB, Chiappinelli KB. Unraveling the molecular pathways of DNA-methylation inhibitors: human endogenous retroviruses induce the innate immune response in tumors. Oncoimmunology. 2015 Dec 29;5(5):e1122160. doi: 10.1080/2162402X.2015.1122160. eCollection 2016. (a review - no acknowledgements allowed by journal)

Presentations

Chiappinelli KB, Stone ML, Topper MJ, Murphy L, Strissel PL, Strick R, Zahnow CA, Baylin SB. Inhibiting DNA methylation causes an interferon response in cancer cells via endogenous retroviruses and recruits immune cells to the tumor microenvironment to sensitize to immune therapy. The American Association for Cancer Research Annual Meeting, New Orleans, LA. April 2016.

Stone ML, Chiappinelli KB, Li H, Murphy L, Topper MJ, Mathios D, Lim M, Baylin SB, Zahnow CA. Epigenetic treatment of ovarian cancer cells increases immune cell recruitment to the tumor microenvironment: Implications for response to immune checkpoint therapy. The American Association for Cancer Research Annual Meeting, New Orleans, LA. April 2016.

Website(s) or other Internet site(s)

Nothing to report

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other Products

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Individuals who have worked on the project

Johns Hopkins University

Name:	Stephen B. Baylin, M.D.
Project Role:	PI (Senior/Key Personnel)
Research Identifier:	N/A

Nearest person month worked:	4
Contribution to Project:	Dr. Baylin oversees all studies and activities conducted under this proposal.
Funding Support:	See Other Support

Name:	Cynthia Zahnow, Ph.D.
Project Role:	Co-Investigator (Senior/Key Personnel)
Research Identifier:	N/A
Nearest person month worked:	2
Contribution to Project:	Dr. Zahnow collaborates with Dr. Baylin on all of the studies in the lab.
Funding Support:	See Other Support

Name:	Drew Pardoll, M.D., Ph.D.
Project Role:	Co-Investigator (Senior/Key Personnel)
Research Identifier:	N/A
Nearest person month worked:	1
Contribution to Project:	Dr. Pardoll works with the Baylin group for all of the studies on how epigenetic therapy can sensitize ovarian cancers to immune checkpoint therapy.
Funding Support:	See Other Support

Name:	Ray-Whay Yen
Project Role:	Research Associate
Research Identifier:	N/A
Nearest person month worked:	8
Contribution to Project:	Ms. Yen is responsible for working with the entire Hopkins group for all of the pre-clinical work on ovarian cancer.
Funding Support:	No change

Name:	Katherine Chiappinelli, Ph.D.
Project Role:	Postdoctoral Fellow / Teal Junior Scientist
Research Identifier:	N/A
Nearest person month worked:	0 (salary is covered by F32 CA183214)
Contribution to Project:	Dr. Chiappinelli has become a real leader in multiple projects as per her accomplishments discussed extensively in the sections above. Her academic growth is discussed in detail in Section 8, Special Reporting.
Funding Support:	No change

Name:	Meredith Stone
Project Role:	Graduate Student
Research Identifier:	N/A
Nearest person month worked:	9
Contribution to Project:	Ms. Stone works along with Dr. Zahnow.
Funding Support:	No change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Yes. See next pages for Drs. Baylin, Zahnow and Pardoll's Other Support.

OTHER SUPPORT

BAYLIN, STEPHEN B.

CURRENT

P50 CA058184 (PI: Baylin)
Title: SPORE in Lung Cancer (Project 1)
Time Commitment: 0.36 calendar
Supporting Agency: NIH/NCI
Procuring Contracting/Grants Officer: Peter Ujhazy
Address of Grants Officer: National Cancer Institute, Building 6116, 6116 Executive Blvd, Rockville, MD 20852
Performance Period: 9/5/1997-11/30/2015
Level of Funding: $242,211 (NCE)
Project's Goal(s): This project involves DNA methylation changes in cancer concerned with their translational implications for lung neoplasms.
Specific Aims: 1. To determine if novel biomarkers added to the current gene panel can enhance the predictive index, for tumor recurrence and death, of a DNA hypermethylation marker system for re-staging of stage I NSCLC. 2. To validate prospectively our findings that changes in promoter DNA methylation can molecularly restage stage I to stage III lung NSCLC and predict early disease recurrence and death. 3. To determine in a prospective controlled clinical trial of stage I NSCLC cancer patients, whether adjuvant epigenetic therapy improves overall and disease-free survival.
Project Overlap or Parallel: No scientific or budgetary overlap.

P50 CA058184 (PI: Baylin)
Title: SPORE in Lung Cancer (Administrative Core)
Time Commitment: 0.36 calendar
Supporting Agency: NIH/NCI
Procuring Contracting/Grants Officer: Peter Ujhazy
Address of Grants Officer: National Cancer Institute, Bldg. 6116-7109, 6116 Executive Blvd, Rockville, MD 20852
Performance Period: 9/5/1997-11/30/2015
Level of Funding: $80,250 (NCE)
Project's Goal(s): This project involves DNA methylation changes in cancer concerned with their translational implications for lung neoplasms.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap.

P30 CA006973 (PI: Nelson)
Title: Regional Oncology Research Center – Senior Leader
Time Commitment: 0.6 calendar
Supporting Agency: NIH/NCI
Procuring Contracting/Grants Officer: Devi Vembu
Address of Grants Officer: National Cancer Institute, Building 6116-700, 6116 Executive Blvd, Rockville, MD 20852
Performance Period: 5/7/1997-4/30/2017
Level of Funding: $12,327 (salary support only)
Project's Goal(s): CORE grant for the Johns Hopkins Oncology Center. Stephen Baylin receives salary support only for leadership and microarray core responsibilities.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap.

R01 ES011858 (PI: Baylin)
Title: DNA Methyltransferase Gene Expression in Colon Cancer
Time Commitment: 0.6 calendar
Supporting Agency: NIH/NIEHS

Procuring Contracting/Grants Officer: Frederick Tyson
Address of Grants Officer: National Institute of Health, Keystone Park 3064, 615 Davis Dr, Durham, NC 27709
Performance Period: 4/1/1991-5/31/2019
Level of Funding: $270,498
Project's Goal(s): Understand, further, the role of altered regulation and patterns of DNA methylation in the progression of colon cancer.
Specific Aims: 1. To determine mechanisms by which SOX17 blocks Wnt activation in CRC evolution. 2. To develop mouse models for CRC evolution based on epigenetic loss of Hic1. 3. To explore specific stages of CRC tumorigenesis mediated by epigenetic silencing of stem/progenitor cell related genes. 4. To define molecular determinants which initiate and/or maintain gene promoter DNA hypermethylation and gene silencing in CRC evolution.
Project Overlap or Parallel: No scientific or budgetary overlap.

U01 HL099775 (PI: Friedman)
Title: Basic and Translational Research of iPSC-Based Hematologic & Vascular Therapies – Project 2
Time Commitment: 0.46 calendar
Supporting Agency: NIH/NHLBI
Procuring Contracting/Grants Officer: Denis Buxton
Address of Grants Officer: NHLBI, Two Rockledge Center, Suite 8216, 6701 Rockledge Dr., Bethesda, MD 20817
Performance Period: 9/30/2009-4/30/2016
Level of Funding: $245,000
Project's Goal(s): This work will provide basic insight into how stem cells can be generated from adult cells and how these cells can be directed to develop into blood cells or blood vessel cells to benefit patients with hematologic or vascular disorders.
Specific Aims: 1. Precisely characterize the degree of cellular transformation observed at early stages of iPSC generation that are caused by reprogramming factor-mediated epigenetic changes, and the role that various factors, and protocols for introducing these factors, play in eliciting these alterations. 2. Determine the molecular mechanisms that induce abnormal epigenetic events during iPSC generation. 3. Determine whether refining use of DAC and TSA during iPSC generation, together with manipulation of DNMTs or other members of the repressive complex, can increase the efficiency of obtaining iPSC, while maximally reducing their tumorigenic potential and enhancing their regeneration potential.
Project Overlap or Parallel: No scientific or budgetary overlap.

90046519 (PI: Baylin/Casero/Zahnow)
Title: Novel Therapies Targeting Epigenetic Silencing of Tumor Suppressors
Time Commitment: 0.12 calendar
Supporting Agency: Samuel Waxman Cancer Research Foundation
Procuring Contracting/Grants Officer: Carole Asher
Address of Grants Officer: 420 Lexington Ave., Suite 825, New York, NY 10170
Performance Period: 7/1/2011-6/30/2016
Level of Funding: $100,000
Project's Goal(s): The goals of this project are: Project 1: To examine newly identified lysine specific demethylase 1 (LSD1) inhibitors in order to advance the understanding of the functioning and targeting of LSD1 for clinical utility. Project 2: To show that epigenetic therapy at very low, non-toxic doses, can dramatically blunt the tumorigenic properties of subpopulations of leukemic and solid tumor populations of "stem-like" cells. Project 3: To demonstrate that low dose epigenetic therapy re-sensitizes drug tolerant breast cancer cells to conventional, single agent chemotherapeutics or targeted therapy.
Specific Aims: 1. To perform, in Kasumi AML cells, and other lines, genome-wide studies of DNA methylation, chromatin and, gene expression patterns, including pathway analyses, for activating and repressive marks in separated populations of tumorigenic CD34+/CD38- versus non-tumorigenic CD34- cells. 2. To examine changes in the above genome-wide patterns induced by low doses of DNA

demethylating and histone deacetylation inhibiting drugs, already shown to inhibit the leukemic engraftment of the whole cell population, alone and together, on the above separated populations. 3. To derive markers for prediction and monitoring of epigenetic therapy from the above studies and which can be studied in primary tumor samples, and patient samples.
Project Overlap or Parallel: No scientific or budgetary overlap.

R01 CA170550 (PI: Laird/Jones)
Title: Epigenetic Drivers of Cancer
Time Commitment: 0.6 calendar
Supporting Agency: University of Southern California
Procuring Grants Officer: Emily Greenspan
Address of Grants Officer: 31 Center Drive, Room 10A-33, Bethesda, MD 20892
Performance Period: 9/1/2012-6/30/2016
Level of Funding: $130,119
Project Goals: We propose to address PQ10: As we improve methods to identify epigenetic changes that occur during tumor development, can we develop approaches to discriminate between "driver" and "passenger" epigenetic events?
Specific Aims: 1. To develop a probabilistic framework for predicting and prioritizing candidate epigenetic driver loci. 2. To select candidate epigenetic drivers of colon, breast, and lung cancer. 3. To functionally test candidate epigenetic drivers of colon, breast, and lung cancer.
Project Overlap or Parallel: No scientific or budgetary overlap.

90052001 (PI: Baylin)
Title: Bringing Epigenetic Therapy to the Management of Ovarian and Other Cancers
Time Commitment: 1.2 calendar
Supporting Agency: Miriam & Sheldon Adelson Medical Research Foundation
Procuring Contracting/Grants Officer: Joseph Bigley
Address of Grants Officer: OncoMethylome Sciences, 2505 Meridian Parkway, Suite 310, Durham, NC 27713
Performance Period: 10/1/2014-9/30/2016
Level of Funding: $436,619
Project's Goal(s): We are embarked on in-depth pre-clinical studies designed to directly bring "epigenetic" therapy, using existing DNA de-methylating agents and histone deactylase inhibitors (HDACi's), to the therapeutic management of advanced ovarian and other cancers.
Specific Aims: N/A
Project Overlap or Parallel: While both of these projects are aimed at taking novel approaches to radically improving the management of women with ovarian cancer, and can inform one another, they fund separate activities vital to this quest. First, while both grants seek to use information to leverage key clinical trials for ovarian cancer, only the Adelson supports activities for implementation of these trials, the bulk of biopsy acquisitions, and any other partial trial costs not otherwise covered. Second, many aspects for studies of host immune cell responses to epigenetic drugs are covered only in the Adelson funding, including work and support of collaborators, and genomics studies, in this effort, while the TEAL funds primarily work for response of ovarian cancer cells. Third, only the TEAL award supports the efforts of the junior investigator mentored by Dr. Baylin to dissect how increased expression of endogenous viruses induced by epigenetic agents elicit up-regulation of ovarian cancer cell viral defense pathways. Lastly, only the Adelson supports work to use epigenetic agents to sensitize ovarian cancer to PARP inhibitors and work, with other collaborators for bring novel epigenetic therapy agents to treatment of ovarian cancer. However, this information can all be brought to bear on work in the TEAL in later years of the grant if indicated.

W81XWH-13-1-0199 (PI: Chan/Baylin)
Title: Targeting Master Regulators of the Breast Cancer Metastasis Transcriptome
Time Commitment: 0.24 calendar

Supporting Agency: Memorial Sloan-Kettering Cancer Center
Procuring Contracting/Grants Officer: Unknown
Address of Grants Officer: Unknown
Performance Period: 7/1/2013-6/30/2018
Level of Funding: $61,555
Project's Goal(s): The Baylin lab will help perform CHIP seq and help analyze the chromatin state data for both the isogenic cell line systems that model differential metastatic ability.
Specific Aims: Aim 1: N/A
Justification: This grant has no overlap with the current proposal.
Project Overlap or Parallel: No scientific or budgetary overlap.

Award ID: W81XWH-14-1-0385(Baylin)
Title: A New Paradigm for the Treatment of Ovarian Cancer: The Use of Epigenetic Therapy to Sensitize Patients to Immunotherapy and Chemotherapy
Effort: 4.2 calendar
Supporting Agency: CDMRP
Name of Procuring Contracting/Grants Officer: Susan Dellinger, Grants Officer
Address of Funding Agency: 1077 Patchel St., Bldg 1077, Fort Detrick, MD 21702
Period of Performance: 09/30/2014-09/29/2019
Level of Funding: $436,208 annual direct costs
Project's Goal: The major goal of this project is to robustly prolong the survival of patients with serous ovarian cancer (OC) through introducing epigenetic therapy paradigms
Specific Aims: 1) To uncover the mechanisms through which epigenetic therapy may, alone, achieve robust, durable responses in patients with advanced ovarian cancer (OC), 2) Study how epigenetic therapy may sensitize OC cells to subsequent chemotherapies, 3) Study how epigenetic therapy may sensitize OC cells to subsequent immunotherapies which targets checkpoints which are driving immune tolerance, 4) Develop new combinations of epigenetic drugs which may provide for the highest level of efficacy for management of OC, 5) Bring all of the above studies to bear on leveraging clinical trials of epigenetic therapy on OC.
Role: PI
Overlap: None

AWARDED SINCE LAST SUBMISSION

R01 CA185357 (PI: Ahuja)
Title: (PQD3) Molecular Profiles associated with Long-Term Survival in pancreas Cancer
Time Commitment: 0.24 calendar
Supporting Agency: NCI
Procuring Contracting/Grants Officer: Unknown
Address of Grants Officer: Unknown
Performance Period: 4/1/2014-3/31/2018
Level of Funding: $341,620
Project's Goal(s): Identify genomic and epigenomic signatures of pancreas cancer patients who have long-term survival using a large dataset.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap.

(PI: Baylin)
Title: The intersection of epigenetic and immune checkpoint therapy
Time Commitment: 0.12 calendar
Supporting Agency: AACR – Phillip A. Sharp Innovation in Collaboration Award
Procuring Contracting/Grants Officer: Unknown
Address of Grants Officer: Unknown
Performance Period: 7/1/2014-12/31/2015 (NCE)

Level of Funding: $227,275
Project's Goal(s): Utilize results from all studies to help craft leveraged clinical trials for lung, melanoma and other cancers which are based on hypotheses derived from the data.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap.

(PI: Baylin)
Title: Clinical trials of epigenetic therapy sensitized patients with advanced non-small cell lung cancer to chemotherapy and immunotherapy
Time Commitment: 0.12 calendar
Supporting Agency: AACR – Jim Toth Sr. Breakthrough Prize in Lung Cancer
Procuring Contracting/Grants Officer: Unknown
Address of Grants Officer: Unknown
Performance Period: 7/1/2014-6/30/2016
Level of Funding: $340,380
Project's Goal(s): N/A
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap.

(PI: Baylin)
Title: Clinical trials of epigenetic therapy in non-small cell lung cancer
Time Commitment: 0.3 calendar
Supporting Agency: Rising Tide Foundation
Procuring Contracting/Grants Officer: Unknown
Address of Grants Officer: Unknown
Performance Period: 1/1/2015-12/31/2018
Level of Funding: $331,360
Project's Goal(s): We are addressing the hypothesis that reversal of cancer-specific DNA methylation and chromatin abnormalities can potently change the management of NSCLC.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap.

(PI: Zambidis)
Title: Functional vascular progenitors from naïve human iPSC
Time Commitment: 0.36 calendar
Supporting Agency: NCI
Procuring Contracting/Grants Officer: Unknown
Address of Grants Officer: Unknown
Performance Period: 5/1/2015-2/29/2020
Level of Funding: $207,500
Project's Goal(s): To develop novel gene targeting and regeneration approaches for treating pediatric and adult vascular disorders using a newly discovered class of human iPSC converted to a ground state of naïve pluripotency.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap.

(PI: Baylin)
Title: VARI-SU2C Epigenetics Dream Team
Time Commitment: 0.12 calendar
Supporting Agency: Van Andel Research Institute
Procuring Contracting/Grants Officer: Unknown
Address of Grants Officer: Unknown
Performance Period: 10/1/2014-9/30/2017
Level of Funding: $190,909
Project's Goal(s): Our Dream Team unites scientists at major cancer research institutions who are poised to propel the early promise of epigenetic therapy in blood malignancies to the forefront of management for patients with breast, colon and lung cancer.

Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap.

(PI: Brahmer/Baylin)
Title: Viral Defense Gene Expression Patterns and Response to Immune Checkpoint Blockade in NSCLC
Time Commitment: 0.24 calendar
Supporting Agency: Bristol-Myers Squibb
Procuring Contracting/Grants Officer: Unknown
Address of Grants Officer: Unknown
Performance Period: 7/1/2015-6/30/2017
Level of Funding: $72,674
Project's Goal(s): This projects seeks to develop a biomarker to predict benefit from immunotherapy and to define if epigenetic modulation synergizes with immune checkpoint blockade.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap.

COMPLETED SINCE LAST SUBMISSION

R01 CA043318 (PI: Baylin)
Title: Methylation of the Calcitonin Gene in Human Tumors
Time Commitment: 0.36 calendar
Supporting Agency: NIH/NCI
Procuring Contracting/Grants Officer: Paul Okano
Address of Grants Officer: National Cancer Institute, Executive Plaza North, Suite 5024, 6130 Executive Blvd., Rockville, MD 20852
Performance Period: 9/30/1986-2/28/2015
Level of Funding: $117,255 (NCE)
Project's Goal(s): Study of the function of a new gene on chromosome 17p13.3 which is hypermethylated in human neoplasia, study of whether the estrogen receptor gene is a tumor suppressor in leukemia, and determination of whether overexpression of the DNA-methyltransferase gene mimics specific tumor suppressor gene inactivation events.
Specific Aims: 1. To explore how cancer specific, DNA hypermethylation of HIC1 may initiate an epigenetic network leading to tumor initiation. 2. To construct in vitro models to determine, precisely, what cellular steps in tumorigenesis can be initiated by epigenetically mediated loss of gene function. 3. To explore interactions between the polycomb group (PcG) of long term gene silencing proteins and SIRT1, DNA methyltransferases, and other key chromatin mediating proteins, which may link transcriptional repression in embryonic stem/progentitor cells and gene vulnerability to abnormal, promoter CpG island, DNA methylation in cancer
Project Overlap or Parallel: No scientific or budgetary overlap.

MDXHealth Incorporated (PI: Herman)
Title: Methylation-Specific PCR Technology (MSP) – Research Agreement
Time Commitment: 0.12 calendar
Supporting Agency: OMS
Procuring Contracting/Grants Officer: Joseph Bigley
Address of Grants Officer: OncoMethylome Sciences, 2505 Meridian Parkway, Suite 310, Durham, NC 27713
Performance Period: 7/1/2003-6/30/2014
Level of Funding: $50,473
Project's Goal(s): N/A
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap.

BioNumerik Pharmaceuticals, Inc. (PI: Baylin)
Title: Collaboration agreement with BioNumerik Pharmaceuticals, Inc.
Time Commitment: 0.12 calendar

Supporting Agency: BioNumerik
Procuring Contracting/Grants Officer: Frederick H. Hausheer, M.D.
Address of Grants Officer: BioNumerik Pharmaceuticals, Inc., 8122 Datapoint Drive, Suite 1250, San Antonio, TX 78229
Performance Period: 11/19/2001-2/09/2015
Level of Funding: $25,236
Project's Goal(s): The overall program will be aimed at the discovery and development of novel therapeutic agents that modulate DNA methylation in cancer. The focus will be to synthesize, patent and test novel chemical entities which target cancer cells with altered DNA methylation.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap.

U24 CA143882 (PI: Laird/Baylin)
Title: The USC-JHU Reference Epigenome Characterization Center
Time Commitment: 0.6 calendar
Supporting Agency: University of Southern California via NIH/NCI
Procuring Contracting/Grants Officer: Joseph Vockley
Address of Grants Officer: National Cancer Institute, Building 31 - Claude D Pepper Building, 3A20, 31 Center Dr.,
Bethesda, MD 20814
Performance Period: 9/29/2009-7/31/2014
Level of Funding: $133,867
Project's Goal(s): Genome Characterization Centers and Genome Data Analysis Center for the Cancer Genome Atlas Research Network (TCGA). The major goal of this project will be to genome wide measurement and characterization of patterns of DNA methylation in human cancers.
Specific Aims: 1. To characterize the DNA methylation status of 27,578 CpG dinucleotides located in 14,495 gene promoters in at least 10,000 human cancer samples and 1,000 control samples using the lllumina Infinium DNA Methylation analysis platform. 2. To transition epigenomic data production in TCGA to whole genome shotgun bisulfite sequence analysis to provide single-base-pair resolution DNA methylation data for TCGA cancer samples**.** 3. To implement quality control and quality assurance measures to ensure that epigenomic data deposited for public dissemination meets rigorous standards
Project Overlap or Parallel: No scientific or budgetary overlap.

SU2C-AACR-CT0109 (PI: Baylin/Jones)
Title: Bringing Epigenetic Therapy to the Forefront of Cancer Management
Time Commitment: 0.6 calendar
Supporting Agency: American Association for Cancer Research
Procuring Contracting/Grants Officer: Dr. Kimberly Sabelko
Address of Grants Officer: AACR, 625 Chestnut Street, 17th Floor, Philadelphia, PA 19106
Performance Period: 12/1/2009-1/31/2015
Level of Funding: $2,811,168 (NCE)
Project's Goal(s): Our Dream Team unites scientists at five major cancer research institutions who are poised to propel the early promise of epigenetic therapy in blood malignancies to the forefront of management for patients with breast, colon, and lung cancer.
Specific Aims: 1. To develop molecular markers which predict, and monitor, the efficacy of cancer epigenetic therapies. 2. To perform clinical trials to bring epigenetic therapy to the forefront of cancer management. 3. To determine whether a key mechanism for efficacy of epigenetic therapy is targeting and exhaustion of self-renewing cancer cells. 4. To develop a clinical trial with a new drug designed to circumvent the instability of 5-AC and DAC. 5. To determine targets in addition to promoter DNA hypermethylation that may be utilized in new cancer epigenetic therapy approaches.
Project Overlap or Parallel: No scientific or budgetary overlap.

U54 CA151838 (PI: Searson)
Title: Center of Cancer Nanotechnology Excellence at Johns Hopkins
Time Commitment: 0.6 calendar
Supporting Agency: NIH/NCI
Procuring Contracting/Grants Officer:
Address of Grants Officer:
Performance Period: 8/25/2010-7/31/2015
Level of Funding: $12,175 (Project 1 – salary support only)
Project's Goal(s): The goal of this Center is to integrate nanotechnology-based diagnostic and therapeutic tools for comprehensive cancer care.
Specific Aims: 1. To develop an integrated sample preparation method combining DNA isolation and bisulfate conversion into a single tube process. 2. To develop a highly sensitive technology enables by convergence of QD-FRET and MSP for detection of DNA methylation. 3. To develop a droplet microfluidic platform for fully integrated sample preparation and QD-FRET sensing, facilitating robust and high-throughput screening of DNA methylation. 4. To evaluate the new methylation screening platform and determine the potential use in early cancer detection and post-therapy monitoring.
Project Overlap or Parallel: No scientific or budgetary overlap.

90052339 (PI: Baylin)
Title: Epigenetic Therapy Sensitizing Breast Cancer to Blockades of DNA Repair
Time Commitment: 0.12 calendar
Supporting Agency: EIF – Entertainment Industry Foundation
Procuring Contracting/Grants Officer: Craig Cichy
Address of Grants Officer: 1201 West 5th Street, Ste T-700, Los Angeles, CA 90017
Performance Period: 10/15/2012-10/15/2014
Level of Funding: $125,000
Project's Goal(s): To understand how epigenetic therapy may regulate DNA repair and thereby sensitize breast cancer cells to therapeutic agent such as PARP inhibitors.
Specific Aims: N/A
Justification: This grant has no overlap with the current proposal.
Project Overlap or Parallel: No scientific or budgetary overlap.

SU2C-AACR-SF1-DT0109 (PI: Baylin/Jones)
Title: Bringing Epigenetic Therapy to the Forefront of Cancer Management
Time Commitment: 0.6 calendar
Supporting Agency: American Association for Cancer Research
Procuring Contracting/Grants Officer: Dr. Kimberly Sabelko
Address of Grants Officer: AACR, 625 Chestnut St., 17th Floor, Philadelphia, PA 19106
Performance Period: 12/01/2012 – 1/31/2015
Level of Funding: $1,100,000 (NCE)
Project's Goal(s): Our Dream Team unites scientists at five major cancer research institutions who are poised to propel the early promise of epigenetic therapy in blood malignancies to the forefront of management for patients with breast, colon, and lung cancer.
Specific Aims: 1) To develop molecular markers which predict, and monitor, the efficacy of cancer epigenetic therapy. 2) To perform clinical trials to bring epigenetic therapy to the forefront of cancer management. 3) To determine whether a key mechanism for efficacy of epigenetic therapy is targeting and exhaustion of self-renewing cancer cells. 4) To develop a clinical trial with a new drug designed to circumvent the instability of 5-AC and DAC. 5) To determine targets in addition to promoter DNA hypermethylation that may be utilized in new cancer epigenetic therapy approaches.
Justification: This grant has no overlap with the current proposal.
Project Overlap or Parallel: No scientific or budgetary overlap.

U24 CA143882 (PI: Laird/Baylin)
Title: The USC-JHU Reference Epigenome Characterization Center
Time Commitment: 0.12 calendar
Supporting Agency: University of Southern California via NIH/NCI
Procuring Contracting/Grants Officer: Joseph Vockley
Address of Grants Officer: National Cancer Institute, Building 31 - Claude D Pepper Building, 3A20, 31 Center Dr.,
Bethesda, MD 20814
Performance Period: 8/1/2013-7/31/2014
Level of Funding: $148,544 (Supplement)
Project's Goal(s): Genome Characterization Centers and Genome Data Analysis Center for the Cancer Genome Atlas Research Network (TCGA). The major goal of this project will be to genome wide measurement and characterization of patterns of DNA methylation in human cancers.
Specific Aims: 1. To characterize the DNA methylation status of 27,578 CpG dinucleotides located in 14,495 gene promoters in at least 10,000 human cancer samples and 1,000 control samples using the lllumina Infinium DNA Methylation analysis platform. 2. To transition epigenomic data production in TCGA to whole genome shotgun bisulfite sequence analysis to provide single-base-pair resolution DNA methylation data for TCGA cancer samples**.** 3. To implement quality control and quality assurance measures to ensure that epigenomic data deposited for public dissemination meets rigorous standards
Project Overlap or Parallel: No scientific or budgetary overlap.

OTHER SUPPORT

ZAHNOW, CYNTHIA A.

ACTIVE

90046519 (PI: Casero/Baylin/Zahnow)
Title: Novel therapies targeting epigenetic silencing of tumor suppressors
Time Commitment: .12 calendar
Supporting Agency: Samuel Waxman Cancer Research Foundation
Procuring Contracting/Grants Officer: Carole Asher
Address of Grants Officer: 420 Lexington Ave., Suite 825, New York, NY 10170
Performance Period: 7/1/2011-6/30/2016
Level of Funding: $50,000
Project's Goal(s): The goals of Dr. Zahnow's project within this Collaborative Grant is to demonstrate that low dose epigenetic therapy re-sensitizes drug tolerant breast cancer cells to conventional, single agent chemotherapeutics or targeted therapy.
Specific Aims: 1. To test whether Azacytidine can sensitize endocrine-resistant breast cancers to anti-estrogen therapy. 2. To continue our investigation of the role of the immune system in the anti-tumorigenic response of breast cancer cells to epigenetic therapy with a special focus on interferon signaling and activation. **Justification:** This grant has no overlap with the current proposal.
Project Overlap or Parallel: No scientific or budgetary overlap.

P30 CA006973 (PI: Nelson)
Title: Regional Oncology Research Center – Resource Director
Time Commitment: 1.2 calendar
Supporting Agency: NIH/NCI
Procuring Contracting/Grants Officer: Devi Vembu
Address of Grants Officer: National Cancer Institute, Building 6116-700, 6116 Executive Blvd, Rockville, MD 20852
Performance Period: 5/7/1997-4/30/2017
Level of Funding: $51,810 (salary support only)
Project's Goal(s): CORE grant for the Johns Hopkins Oncology Center. Dr. Zahnow receives salary support only for serving as the Director of the Animal Facility and administrative duties to the Oncology Center.
Specific Aims: N/A
Justification: This grant has no overlap with the current proposal.
Project Overlap or Parallel: No scientific or budgetary overlap.

R01 CA170550 (PI: Laird/Jones)
Title: Epigenetic Drivers of Cancer
Time Commitment: 1.2 calendar
Supporting Agency: University of Southern California
Procuring Contracting/Grants Officer: Emily Greenspan
Address of Grants Officer: 31 Center Dr., Rm. 10A-33, Bethesda, MD 20892
Performance Period: 9/01/2012-6/30/2016
Level of Funding: $130,119
Project Goals: We propose to address PQ10: As we improve methods to identify epigenetic changes that occur during tumor development, can we develop approaches to discriminate between "driver" and "passenger" epigenetic events?
Specific Aims: 1) To develop a probabilistic framework for predicting and prioritizing candidate

epigenetic driver loci 2) To select candidate epigenetic drivers of colon, breast, and lung cancer. 3) To functionally test candidate epigenetic drivers of colon, breast, and lung cancer.
Justification: This grant has no overlap with the current proposal.
Project Overlap or Parallel: No scientific or budgetary overlap.

90052001 (PI: Baylin)
Title: Bringing Epigenetic Therapy to the Management of Ovarian and Other Cancers
Time Commitment: 2.4 calendar
Supporting Agency: Miriam & Sheldon Adelson Medical Research Foundation
Procuring Contracting/Grants Officer: Marissa White
Address of Grants Officer: 300 First Avenue, Suite 330, Needham, MA 02494
Performance Period: 10/01/2014-9/30/2016
Level of Funding: $431,895
Project Goals: We are embarked on in-depth pre-clinical studies designed to directly bring "epigenetic" therapy, using existing DNA de-methylating agents and histone deactylase inhibitors (HDACi's), to the therapeutic management of advanced ovarian and other cancers.
Specific Aims: N/A
Justification: This grant has no overlap with the current proposal.
Project Overlap or Parallel: While both of these projects are aimed at taking novel approaches to radically improving the management of women with ovarian cancer, and can inform one another, they fund separate activities vital to this quest. First, while both grants seek to use information to leverage key clinical trials for ovarian cancer, only the Adelson supports activities for implementation of these trials, the bulk of biopsy acquisitions, and any other partial trial costs not otherwise covered. Second, many aspects for studies of host immune cell responses to epigenetic drugs are covered only in the Adelson funding, including work and support of collaborators, and genomics studies, in this effort, while the TEAL funds primarily work for response of ovarian cancer cells. Third, Only the TEAL award supports the efforts of the junior investigator mentored by Dr. Baylin to dissect how increased expression of endogenous viruses induced by epigenetic agents elicit up-regulation of ovarian cancer cell viral defense pathways. Lastly, only the Adelson supports work to use epigenetic agents to sensitize ovarian cancer to PARP inhibitors and work, with other collaborators for bring novel epigenetic therapy agents to treatment of ovarian cancer. However, this information can all be brought to bear on work in the TEAL in later years of the grant if indicated.

AWARDED SINCE LAST SUBMISSION

(PI: Baylin)
Title: The intersection of epigenetic and immune checkpoint therapy
Time Commitment: 0.6 calendar
Supporting Agency: AACR – Phillip A. Sharp Innovation in Collaboration Award
Procuring Contracting/Grants Officer: Unknown
Address of Grants Officer: Unknown
Performance Period: 7/1/2014-12/31/2015
Level of Funding: $227,275
Project's Goal(s): Utilize results from all studies to help craft leveraged clinical trials for lung, melanoma and other cancers which are based on hypotheses derived from the data.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap.

(PI: Baylin)
Title: Clinical trials of epigenetic therapy in non-small cell lung cancer
Time Commitment: 0.3 calendar

Supporting Agency: Rising Tide Foundation
Procuring Contracting/Grants Officer: Unknown
Address of Grants Officer: Unknown
Performance Period: 1/1/2015-12/31/2018
Level of Funding: $331,360
Project's Goal(s): We are addressing the hypothesis that reversal of cancer-specific DNA methylation and chromatin abnormalities can potently change the management of NSCLC.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap.

(PI: Brahmer/Baylin)
Title: Viral Defense Gene Expression Patterns and Response to Immune Checkpoint Blockade in NSCLC
Time Commitment: 1.2 calendar
Supporting Agency: Bristol-Myers Squibb
Procuring Contracting/Grants Officer: Unknown
Address of Grants Officer: Unknown
Performance Period: 7/1/2015-6/30/2017
Level of Funding: $72,674
Project's Goal(s): This project seeks to develop a biomarker to predict benefit from immunotherapy and to define if epigenetic modulation synergizes with immune checkpoint blockade.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap.

COMPLETED SINCE LAST SUBMISSION

90038725 (PI: Baylin)
Title: The Lee Jeans Translational Breast Cancer Research Program
Time Commitment: 0.6 calendar
Supporting Agency: EIF – Entertainment Industry Foundation
Procuring Contracting/Grants Officer: Bobby Fergerstrom
Address of Grants Officer: 1201 West 5th Street, Ste T-700, Los Angeles, CA 90017
Performance Period: 7/1/2009-6/30/2014
Level of Funding: $159,090 (NCE)
Project's Goal(s): This project aims to extrapolate basic mechanisms underlying the efficacy of epigenetic therapy in pre-leukemic and leukemic states to studies of breast cancer cells representing the various subtypes of this disease and to rapidly implement these findings into clinical trials.
Specific Aims: 1) To expand our analysis of how breast cancer cell lines and primary tissue from breast cancer patients respond to low doses of the DNA demethylating agent 5-azacitidine (Vidaza, 5-AC, AZA), and the histone deacetylase inhibitor MS-275 (Entinostat), alone and in combination. 2) To determine how Vidaza and/or Entinostat may be used to re-sensitize drug tolerant breast cancer cells to therapies they have become resistant to. 3) To determine which chemotherapy regimen is most effective when used in combination with Vidaza and Entinostat.
Justification: This grant has no overlap with the current proposal.
Project Overlap or Parallel: No scientific or budgetary overlap.

SU2C-AACR-SF1-DT0109 (PI: Baylin/Jones)
Title: Bringing Epigenetic Therapy to the Forefront of Cancer Management
Time Commitment: 0.6 calendar
Supporting Agency: American Association for Cancer Research
Procuring Contracting/Grants Officer: Dr. Kimberly Sabelko
Address of Grants Officer: AACR, 625 Chestnut St., 17th Floor, Philadelphia, PA 19106
Performance Period: 12/01/2012 – 1/31/2015

Level of Funding: $1,100,000 (NCE)
Project's Goal(s): Our Dream Team unites scientists at five major cancer research institutions who are poised to propel the early promise of epigenetic therapy in blood malignancies to the forefront of management for patients with breast, colon, and lung cancer.
Specific Aims: 1) To develop molecular markers which predict, and monitor, the efficacy of cancer epigenetic therapy. 2) To perform clinical trials to bring epigenetic therapy to the forefront of cancer management. 3) To determine whether a key mechanism for efficacy of epigenetic therapy is targeting and exhaustion of self-renewing cancer cells. 4) To develop a clinical trial with a new drug designed to circumvent the instability of 5-AC and DAC. 5) To determine targets in addition to promoter DNA hypermethylation that may be utilized in new cancer epigenetic therapy approaches.
Justification: This grant has no overlap with the current proposal.
Project Overlap or Parallel: No scientific or budgetary overlap.

90052339 (PI: Baylin)
Title: Epigenetic Therapy Sensitizing Breast Cancer to Blockades of DNA Repair
Time Commitment: 0.12 calendar
Supporting Agency: EIF – Entertainment Industry Foundation
Procuring Contracting/Grants Officer: Craig Cichy
Address of Grants Officer: 1201 West 5th Street, Ste T-700, Los Angeles, CA 90017
Performance Period: 10/15/2012-10/14/2014
Level of Funding: $125,000 (NCE)
Project's Goal(s): To understand how epigenetic therapy may regulate DNA repair and thereby sensitize breast cancer cells to therapeutic agent such as PARP inhibitors.
Specific Aims: N/A
Justification: This grant has no overlap with the current proposal.
Project Overlap or Parallel: No scientific or budgetary overlap.

OTHER SUPPORT

PARDOLL, DREW M.

ACTIVE

Award ID: P50CA098252 (Wu)
Title: SPORE in Cervical Cancer
Effort: 0.36 calendar months
Supporting Agency: NIH/NCI
Name of Procuring Contracting/Grants Officer: Jason Gill
Address of Funding Agency: 9609 Medical Center Drive, Rockville, MD 20850
Performance Period: 09/01/04 – 08/31/19
Level of Funding: $1,668,395 annual direct costs
Project's Goal: The development research program role is to identify and select pilot projects with potential for development into full- fledged translational research avenues, collaborations, and new methodologies for integration into other research projects based on the described review criteria.
Specific Aims: 1) Provide initiating funds for novel explorations related to cervical cancer. 2) Integrate the awardee into the SPORE community by participation in monthly meetings, group communications, and opportunities for expanded funding and for collaborations. 3) Review progress and recommend avenues for continuation of successful projects
Role: Co- Director, Developmental Research Program
Overlap: None

Award ID: P30CA06973 (Nelson)
Title: Regional Oncology Research
Center
Effort: 0.6 calendar months
Supporting Agency: NIH/NCI
Name of Procuring Contracting/Grants Officer: Jason Gill
Address of funding agency: 9609 Medical Center Drive, Rockville, MD 20850
Performance Period: 08/09/2012-04/30/2017
Level of Funding: $20,276*
Project's Goal: The major goal of this project is to support research programs and shared resources at the National Cancer Institute Designated Cancer Center. The central goal of the Cancer Immunology program is the development of new effective cancer immunotherapies that are based on understanding the molecular recognition and regulation.
Specific Aims: N/A
Role: Co-Program Leader for Cancer Immunology (*salary support only)
Overlap: None

Award ID: 90054364 (Pardoll)
Title: International Immuno-Oncology Network (IION) Resource Model
Effort: 1.2 calendar months
Supporting Agency: Bristol- Myers Squibb Co
Name of Procuring Contracting/Grants Officer: Les Enterline
Address of Funding Agency: Route 206 and Providence Line Road, Princeton, NJ 08543
Period of Performance: 05/07/2013-05/06/2017
Level of Funding: $486,987 annual direct cost

Project's Goal: The major goals of this project are to dissect the tumor immune microenvironment in the context of therapy with immune checkpoint blockade and to monitor tumor burden using circulating tumor DNA (ctDNA)
Specific Aims: 1.) Analyze immune-inhibitory networks in resected tumors employing 3 techniques for geographic localization: (i) IHC, (ii) amplified ISH, and (iii) qRT-PCR analysis of laser capture micro-dissected (LCM) regions of leukocytic infiltration. 2.) Complementary to the studies in 1, we will sort myeloid, lymphoid and cancer cells from freshly dissociated tumors in cases where enough tumor is available, allowing analysis by flow cytometry and mRNA profiling of cellular subsets for co-expression of inhibitory ligands, receptors and druggable metabolic enzymes. 3.) Using qRT-PCR, amplified ISH and multiplex ELISA, we will analyze the spectrum of cytokines within the tumor microenvironment.
Role: PI
Overlap: None

Award ID: 273686 (Pardoll)
Title: CTLA-4 and anti-PD1 blockade: Correlative assessments for discovery
Effort: .36 calendar months
Supporting Agency: Bristol-Myers Squibb Co
Name of Procuring Contracting/Grants Officer: Les Enterline
Address of Funding Agency: Route 206 and Providence Line Road, Princeton, NJ 08543
Period of Performance: 07/10/2013-07/09/2016
Level of Funding: $125,000 annual direct costs
Projects Goal: The major goal of this project is to help guide optimal therapeutic combinations of co-inhibitory agents, to identify novel therapeutic Immune modulatory targets, and to predict, understand and overcome disease resistance.
Specific Aims: 1. Characterize changes in tumor infiltrating lymphocytes (TILs) and circulating peripheral blood cells from serially acquired tumor and blood samples from patients with therapeutic response to ipi, nivo and combination therapy with comparison to non-responders. 2. Characterize changes in metastatic melanoma cells, myeloid cells and tumor aSSOCiated fibroblasts from tumor samples from patients with therapeutic response 10 ipi, nivo and combination therapy with comparison to non-responders. 3. Compare finding from pre- and post-therapy specimens from patients treated with ipi and nivo as single agents vs combination therapy to identify unique potential biomarkers predictive of therapeutic response to combinatorial blockade.
Role: PI
Overlap: Overlaps with grant below. This is an Academic-Industry sponsored award with MRA being the prime sponsor and BMS being the industry sponsor. Each sponsor provides 50% support for the project.

Award ID: 273686
Title: CTLA-4 and anti-PD1 blockade: Correlative assessments for discovery
Effort: .36 calendar months
Supporting Agency: Memorial Sloan Kettering Cancer Center (Prime sponsor, Melanoma Research Alliance)
Name of Procuring Contracting/Grants Officer: Richard K. Naum
Address of Funding Agency: 1275 York Ave, New York, New York 10065
Performance Period: 07/10/2013-07/09/2016
Level of Funding: $125,000 annual direct costs
Project's Goal: The major goal of this project is to help guide optimal therapeutic combinations of co-inhibitory agents, to identify novel therapeutic Immune modulatory targets, and to predict, understand and overcome disease resistance

Specific Aims: 1. Characterize changes in tumor infiltrating lymphocytes (TILs) and circulating peripheral blood cells from serially acquired tumor and blood samples from patients with therapeutic response to ipi, nivo and combination therapy with comparison to non-responders. 2. Characterize changes in metastatic melanoma cells, myeloid cells and tumor aSSOCiated fibroblasts from tumor samples from patients with therapeutic response 10 ipi, nivo and combination therapy with comparison to non-responders. 3. Compare finding from pre- and post-therapy specimens from patients treated with ipi and nivo as single agents vs combination therapy to identify unique potential biomarkers predictive of therapeutic response to combinatorial blockade.
Role: PI
Overlap: Overlaps with grant above. This is an Academic-Industry sponsored award with MRA being the prime sponsor and BMS being the industry sponsor. Each sponsor provides 50% support for the project.

Award ID: SU2C-AACR-DT10
Title: Immunologic Checkpoint Blockade and Adoptive Cell Transfer in Cancer Therapy
Effort: 2.4 calendar months (20% effort, 10% salary support)
Supporting Agency: MD Anderson Cancer Center -Prime Sponsor-AACR (SU2C)
Name of Procuring Contracting/Grants Officer: Melinda Cotten
Address of Funding Agency: 1515 Holcombe Blvd, Houston, TX 77030-4000
Performance Period:3/1/2013-02/28/2016
Level of Funding: $468,182 annual direct cost
Project's Goal: The major goal of this project is to 1.) develop an increased understanding of immune cells and pathways within the tumor microenvironment that contribute to tumor resistance vs. rejection, 2.) identify the antigenic targets of both T and B cells response to checkpoint blockade, including unique neoantigens that arise as a result of missense mutations in the tumors and 3.) develop rationale combinatorial treatment regiments.
Specific Aims: Aim 1: Interrogation of the immune responses within the tumor microenvironment before and after treatment with immune checkpoint blockade. Aim 2: Interrogation of the targets of T and B cell responses after checkpoint blockade. Aim 3: Development of combinatorial cancer therapies based on checkpoint blockade.
Role: PI
Overlap: None

Award ID: N/A (Pardoll)
Title: CTLA-4 and anti-PD1 blockade: Correlative assessments for discovery
Effort: .12 calendar months
Supporting Agency: Bristol-Myers Squibb Co
Name of Procuring Contracting/Grants Officer: Les Enterline
Address of Funding Agency: Route 206 and Providence Line Road, Princeton, NJ 08543
Period of Performance: 07/10/2013-07/09/2016
Level of Funding: $125,000 annual direct costs
Projects Goal: The major goal of this project is to help guide optimal therapeutic combinations of co-inhibitory agents, to identify novel therapeutic Immune modulatory targets, and to predict, understand and overcome disease resistance.
Specific Aims: 1. Characterize changes in tumor infiltrating lymphocytes (TILs) and circulating peripheral blood cells from serially acquired tumor and blood samples from patients with therapeutic response to ipi, nivo and combination therapy with comparison to non-responders. 2. Characterize changes in metastatic melanoma cells, myeloid cells and tumor aSSOCiated fibroblasts from tumor samples from patients with therapeutic response 10 ipi, nivo and combination therapy with comparison to non-responders. 3. Compare finding from pre- and post-

therapy specimens from patients treated with ipi and nivo as single agents vs combination therapy to identify unique potential biomarkers predictive of therapeutic response to combinatorial blockade.
Role: PI
Overlap: Overlaps with grant below. This is an Academic-Industry sponsored award with MRA being the prime sponsor and BMS being the industry sponsor. Each sponsor provides 50% support for the project.

Award ID: W81XWH-14-1-0385(Baylin)
Title: A New Paradigm for the Treatment of Ovarian Cancer: The Use of Epigenetic Therapy to Sensitize Patients to Immunotherapy and Chemotherapy
Effort: .36 cal months
Supporting Agency: CDMRP
Name of Procuring Contracting/Grants Officer: Susan Dellinger, Grants Officer
Address of Funding Agency: 1077 Patchel St., Bldg 1077, Fort Detrick, MD 21702
Period of Performance: 09/30/2014-09/29/2019
Level of Funding: $436,208 annual direct costs
Project's Goal: The major goal of this project is to robustly prolong the survival of patients with serous ovarian cancer (OC) through introducing epigenetic therapy paradigms
Specific Aims: 1) To uncover the mechanisms through which epigenetic therapy may, alone, achieve robust, durable responses in patients with advanced ovarian cancer (OC) 2) Study how epigenetic therapy may sensitize OC cells to subsequent chemotherapies 3) Study how epigenetic therapy may sensitize OC cells to subsequent immunotherapies which targets checkpoints which are driving immune tolerance 4) Develop new combinations of epigenetic drugs which may provide for the highest level of efficacy for management of OC
5) Bring all of the above studies to bear on leveraging clinical trials of epigenetic therapy on OC
Role: Co-Investigator
Overlap: None

AWARDED SINCE LAST SUBMISSION

Award ID: 90062513 (Pardoll)
Title: The role of neuritin/sema4 interactions to promote expansion and persistence of Tregs
Effort: 1.2 calendar Months
Supporting Agency: Potenza Therapeutics, Inc
Name of Procuring Contracting/Grants Officer: Daniel J. Hicklin, PhD
Address of Funding Agency: 1030 Massachusetts Avenue, Suite 210, Cambridge, MA 02138
Performance Period: 04/01/2015-03/31/2017
Level of Funding: $348,837 annual direct costs
Project goal: The major goal of this project is to further delineate the role of the neuritin/sema4 interaction in promoting the expansion and persistence of Tregs
Specific Aims: 1) Generate panel of monoclonal antibodies with high affinity for neuritin. 2) Define in vitro and in vivo activity of these antibodies, particularly regarding Treg maintenance and function. Benchmark against Neutitin KO. 3) Define in vitro and in vivo activity of peptides that block Neuritin- Seama4A/D interaction and recombinant Neuritin protein. 4) Confirming and mapping the interaction between neuritin and semaphoring 4D. 5) Generate and screen for blocking antibodies which disrupt the neuritin/sema4D interaction. 6) Examine the expression of neuritin on Tregs in human peripheral blood and tumor infiltrating leukocytes. 7) Pharmacology studies to examine the activity of mAbs targeting the neuritin/sema4 interaction in several murine models of cancer (alone or in combination with other immunotherapies)
Role: PI

Overlap: None

Award ID: 308121 (Vogelstein)
Title: Mutational Density and Response to Immunotherapy with Checkpoint Blockade
Effort: 1.2 Calendar months
Supporting Agency: Melanoma Research Alliance
Name of Procuring Contracting/Grants Officer: Laura Brockway-Lunardi, Ph.D.
Address of Funding Agency: 1101 New York Avenue, Suite 620, Washington, DC 20005
Period of Performance: 05/15/2014-05/14/2017
Level of Funding: $300,000 annual direct costs
Projects Goal: The goal of this project is to lay the groundwork for a biomarker to predict response to anti-PD-1 antibodies and also for the generation of personalized melanoma vaccines that could be used in combination with anti-PD-1 therapy.
Specific Aims: 1.) Determine whether overall mutational load in melanoma correlates with PD-1 ligand (PD-L1 and PD-L2) expression and clinical response to anti-PD-1 treatment. 2.) Using algorithms for HLA binding, proteasome processing and TAP transport, determine whether predicted mutation-derived neoepitopes correlate with PD-1 ligand expression and clinical response to anti-PD-1 treatment and 3.) In selected cases, analyze T cell responses to predicted *neoepitopes* from peripheral blood lymphocytes and compare them with responses to epitopes from index *shared* melanosomal and cancer-testes antigens.
Role: Co-investigator
Overlap: None

Award ID: BMSC192 (Topalian/Pardoll)
Title: Analysis of PD-1 Blockade in Virus-Associated Cancers
Effort: **.**24 Calendar months
Supporting Agency: Bristol Myers Squibb Co
Name of Procuring Contracting/Grants Officer: Les Enterline
Address of Funding Agency: Route 206 and Providence Line Road, Princeton, NJ 08543
Period of Performance: 11/01/2014-10/31/2015
Level of Funding: $168,042 annual direct costs
Projects Goal: The major goal of this project is to characterize immune cell types and the expression of immune-modulating molecules (PD-1, PD-L1 and others) in the microenvironment of select cancers associated with EBV or HPV
Specific Aims: N/A
Role: PI
Overlap: None

Award ID: N/A (Pardoll)
Title: Analysis of novel immunomodulatory ligands and receptors
Effort: .6 calendar months
Supporting Agency: Compugen Ltd.
Name of Procuring Contracting/Grants Officer: Anat Cohen-Dayag, Ph.D.
Address of Funding Agency: 72 Pichas Rosen St., Tel Aviv 69512, Israel
Period of Performance: 12/17/2014-11/30/2019
Level of Funding: $331,395 annual direct costs
Project's Goal: The major goal of this project is to study the immunobiology and cancer immunotherapy relevance of multiple novel gene products identified as potentially immunomodulatory
Specific Aims: 1) Determine in-house phage display vs conventional hybridoma depending on level of conservation of molecule across species. 2) Expression studies in mice and humans-define

target's expression tumor components of the TME, sorted cell populations, purified tumor infiltrates, myeloid and lymphocyte human-on selected targets. 3) In vitro testing of murine and human antibodies and Fc fusion molecules 4)Antibody/Recombinant Fc fusion experiments with emphasis on antibodies 5) Therapeutic synergy experiments
Role: PI
Overlap: None

Award ID: 305021 (Topalian)
Title: Crossroads of Genetic and Immunologic Heterogeneity of Melanoma Metastasis
Effort: .24 calendar months* effort, no salary
Supporting Agency: Melanoma Research Alliance
Name of Procuring Contracting/Grants Officer: Laura Brockway-Lunardi, Ph.D.
Address of Funding Agency: 1101 New York Avenue, Suite 620, Washington, DC 20005
Period of Performance: 05/15/2014-05/14/2017
Level of Funding: $75,000 annual direct costs
Project's Goal: The major goal of this project is to characterize interactions between heterogeneous genetic and immunological factors in melanoma, by studying primary and metastatic tumors obtained through a rapid autopsy program
Specific Aims: 1) Establish a rapid autopsy biospecimen bank of primary and metastatic melanoma lesions from 8-10 patients. 2) Characterize genetic features of tumor clonal evolution through space (anatomic location) and time (primary lesion to metastasis). 3) Explore the immunological heterogeneity of metastasis. 4) Correlate genetic and immunological signatures in order to understand factors driving tumor-induced immunosuppression and progression
Role: Co-Investigator
Overlap: None

Award ID: N/A (Pardoll)
Title: The role of neuritin/sema4 interactions to promote expansion and persistence of Tregs
Effort: 1.2 cal months
Supporting Agency: Potenza Therapeutics
Name of Procuring Contracting/Grants Officer: Daniel J. Hicklin, PhD
Address of Funding Agency: 1030 Massachusetts Avenue, Suite 210, Cambridge, MA 02138
Period of Performance: 04/01/2015-03/31/2017
Level of Funding: $348,837 annual direct costs
Project's Goal: The major goal of this project is to further delineate the role of the neuritin/sema4 interaction in promoting the expansion and persistence of Tregs
Specific Aims: 1) Generate panel of monoclonal antibodies with high affinity for neuritin 2) Define in vitro and in vivo activity of these antibodies, particularly regarding Treg maintenance and function. Benchmark against Neutitin KO. 3) Define in vitro and in vivo activity of peptides that block Neuritin- Seama4A/D interaction and recombinant Neuritin protein. 4) Confirming and mapping the interaction between neuritin and semaphoring 4D. 5) Generate and screen for blocking antibodies which disrupt the neuritin/sema4D interaction. 6) Examine the expression of neuritin on Tregs in human peripheral blood and tumor infiltrating leukocytes. 7) Pharmacology studies to examine the activity of mAbs targeting the neuritin/sema4 interaction in several murine models of cancer (alone or in combination with other immunotherapies)
Role: PI
Overlap: None

COMPLETED SINCE LAST SUBMISSION

Award ID: R01CA151393 (Pardoll; Sears contact PI)
Title: Enterotoxigenic Bacteroides Fragilis: A Bacterial Promoter of Colon Oncogenesis
Effort: 1.2 calendar months
Supporting Agency: NIH/NCI
Name of Procuring Contracting/Grants Officer: Connie Murphy
Address of Funding Agency: National Cancer Institute, 8490 Progress Drive, Frederick, MD 21701
Performance Period: 09/02/10 – 07/31/15
Level of Funding: $296,951 annual direct cost
Project's Goal: The major goal of this project is to focus on analysis of the overall colonic microbiome and seek to determine whether there are general microbiome signatures that correlate with defined colonic immune responses and are associated with human colon cancer and proximal and distal flanking normal tissue.
Specific Aims: 1. To analyze the association of ETBF (together with specific isotypes of BFT) and colon cancer. 2. To identify Stat3 activation in colon cancer and define its association with intratumoral immune responses, particularly Th17 responses
Role: Co-PI
Overlap: None

Award ID: R01AI089830 (Pardoll)
Title: The Role of EOS in Regulatory T-Cell Biology
Effort: 1.32 calendar months
Supporting Agency: NIH/NIAID
Name of Procuring Contracting/Grants Officer: Mildred J. Qualls
Address of Funding Agency: 6700B Rockledge Drive, Bethesda, MD 20817
Performance Period: 07/01/10 - 06/30/15
Level of Funding: $232,650 annual direct cost
Project's Goal: The major goal of this project is to study the role of EOS in Regulatory T-Cell Biology
Specific Aims: 1.) Elucidate the role of metabolic stimuli that affect NADH/NAD balance in Eos mediated gene silencing via the CtBP1 complex. Our preliminary data demonstrate that the Rossman domain in CtBP1 may endow Treg cells to sense metabolic cues via the NADH/NAD redox balance. This hypothesis will be explored by analyzing NADH/NAD ratios in Treg, using drugs that alter the NADH/NAD balance and testing mutants of CtBP1 that fail to bind NAD(H). 2.) Study the regulation of Eos expression in Treg cells by microRNAs. Our preliminary data suggest that iR17-92 regulates Eos levels via RNA interference. We will explore the role of this and other candidate microRNAs in Eos regulation in Treg. 3) Study the consequences of Eos deletion to Treg cell homeostasis, differentiation and adaptive Treg cell development. We will employ both siRNA knockdown and conditional knockout of Eos to explore its role in homeostasis, differentiation and capacity of both natural and adaptive Treg to modulate Th1, Th2 and Th17 responses using well established *in vivo* systems.
Role: PI
Overlap: None

Award ID: R01CA151325 (Sears)
Title: Mechanisms of TH17 Inflammation-Induced Colon Carcinogenesis
Effort: 1.2 calendar months
Support Agency: NIH/NCI
Name of Procuring Contracting/Grants Officer: Cammie La

Address of Funding Agency: 9609 Medical Center Drive, Rockville, MD 20850
Performance Period: 07/06/2010 – 04/30/2015
Level of Funding: $190,950 annual direct cost
Project's Goal: The major goal of this project is to study the immune and genetic mechanisms by which a newly recognized common human stool bacterium called exterotoxigenic Bacteroides fragilis triggers colon tumors in mice, providing new insights into how colon cancer develops and potential new approaches to colon cancer therapy.
Specific Aims: 1) Define the components of the colonic Stat3/Th17 immune response that contribute to induction of colon tumorigenesis by ETBF. We will use two major approaches to address this question. A. We will identify the contribution of Stat3 activation in distinct cellular compartments to ETBF colon tumorigenesis. B. We will determine the contribution of specific Th17 cytokines in the induction of colon tumorigenesis by ETBF. 2) Analyze the effects of ETBF Th17 colitis on the genetic and epigenetic characteristics of induced colon tumors.
Role: Co-Investigator
Overlap: None

Award ID: R01CA142779 (Pardoll)
Title: B7-H1/PD1 modulation in cancer therapy
Effort: .96 calendar months
Supporting Agency: NIH/NCI
Name of Procuring Contracting/Grants Officer: Jason Gill
Address of Funding Agency: 9609 Medical Center Drive, Rockville, MD 20850
Performance Period: 06/21/2010 – 05/31/2015
Level of Funding: $266,585 annual direct cost
Project's Goal: The major goal of this project is to study B7-H1/PD1 modulation in cancer therapy.
Specific Aims: 1): Evaluate B7-H1 and PD-1 protein expression as independent markers of cancer progression. 2): Define mechanisms that regulate B7-H1 expression by tumors and PD-1 expression by T cells. 3): Dissect and manipulate B7-H1-mediated retrograde signaling in tumor cells ("B7-H1 molecular shield"). 4): Characterize immunological mechanisms underlying the clinical effects of B7-H1/PD-1 blockade in cancer therapy.
Role: PI
Overlap: None

Award ID: 90038966 (Pardoll)
Title: Combinatorial Immunotherapy for Melanoma with B7H1/PD-1 Checkpoint Blockade
Effort: 1.68 calendar months
Supporting Agency: Melanoma Research Alliance
Name of Procuring Contracting/Grants Officer: Laura Brockway-Lunardi, Ph.D.
Address of Funding Agency: 1101 New York Avenue, Suite 620, Washington, DC 20005
Performance Period: 7/15/09 – 08/31/14
Level of Funding: $500,000 annual direct cost
Project's Goal: The major goal of the project is to evaluate the combination of a GM-CSF transduced melanoma vaccine together with anti-PD1 blockade in the treatment of melanoma.
Specific Aim: N/A
Role: PI
Overlap: None

Award ID: U19AI088791 (Cox)
Title: Baltimore Acute Hepatitis C Cooperative Center
Effort: 0.36 calendar months

Supporting Agency: NIH/NIAID
Name of Procuring Contracting/Grants Officer: Samantha J. Tempchin
Address of Funding Agency: 6700B Rockledge Drive, Bethesda, MD 20817
Performance Period: 04/15/10 – 03/31/15
Level of Funding: $435,436 annual direct cost
Project's Goal: This grant is a multi-project grant permitting maintenance of a cohort of subjects at risk for HCV infection, studying humoral responses to HCV, and developing a unique set of in vitro and in vivo assays to assess the effects of immunomodulatory agents on HCV specific T cells.
Specific Aims: 1) To perform a set of in vitro functional analyses assessing the capacity of HCV specific CD8 T cells of various previously characterized phenotypes to produce relevant effector cytokines and to perform killer functions. This analysis will use blocking antibodies and agonists for selected inhibitory, survival and costimulatory receptors thought to play a potential role in regulating T cell responsiveness in the setting of chronic HCV infection. 2) To develop and characterize a novel in vivo cytotoxic lymphocyte (CTL) assay for functional analysis of HCV specific CD8 cells using adoptive transfer into NOD/SCID/-YC-/- (NOG) mice. This assay will allow us to directly analyze the in vivo functional effects of antibodies and/or cytokines targeted at potentially relevant cell membrane receptors on human HCV specific CD8 T cells. Using specific antagonist antibodies, candidate molecular determinants of CDS T cell unresponsiveness will be interrogated in this novel in vivo system in which human T cells from HCV infected patients are adoptively transferred into receptive immunodeficient mice. Outcomes of this interrogation will have direct translational relevance to the immunotherapy of chronic HCV infection as well as enhancing understanding of T cell impairment associated with persistent infection.
Role: Co-Investigator Project 1
Overlap: None

Award ID: 90053935 (Pardoll)
Title: Development of *STINGVAX*, Cyclic Dinucleotide Formulated GVAX Cancer Vaccine, as a Novel Cancer Immunotherapeutic Agent
Effort: 0.12 calendar months
Support Agency: Aduro Biotech
Name of Procuring Contracting/Grants Officer: Thomas Dubensky
Address of Funding Agency: 626 Bancroft Way, 3C, Berkeley, CA 94710-2224
Performance Period: 03/01/2013-02/28/2015
Level of Funding: $150,000 annual direct cost
Project's Goal: To provide critical preclinical studies to optimize STINGVAX and to define a treatment regimen for clinical use.
Specific Aims 1): To optimize the STINGVAX formulation with optimal *in vivo* tumor regression potential. 2): To establish the mechanism of action of STINGVAX in its ability to activate antigen presenting cell. 3): To assess the activation potential of the various CDN species on human dendritic cells
Role: PI
Overlap: None

Award ID: 90054405 (Sears)
Title: Induction of Human Colon Cancer by Bacteroides fragilis Toxin(BFT)-producing Bacteroides Species
Effort: 0.6 calendar months
Supporting Agency: Institut Merieux
Name of Procuring Contracting/Grants Officer: Christine M'Rini
Address of Funding Agency: 17 Rue Bourgelat-69002 Lyon (France)

Performance Period: 04/22/2013-04/22/2015
Level of Funding: $237,258 annual direct cost
Project's Goal: The major goal of this project is to validate the association of bft-expressing Bacteroides species with CRC and further, to identify targets for development of sensitive and specific diagnostics to identify patients at potential high risk for CRC
Specific Aim: N/A
Role: PI
Overlap: None

Award ID: 90056159 (Pardoll)
Title: Effects of mutation specific targeted TKI on tumor immunity and PD-1 ligand expression in NSCLC
Effort: .12 calendar months
Supporting Agency: Bristol-Myers Squibb Co
Name of Procuring Contracting/Grants Officer: Les Enterline
Address of Funding Agency: Route 206 and Providence Line Road, Princeton, NJ 08543
Period of Performance: 08/24/2013-08/23/2014
Level of Funding: $37,791 annual direct costs
Projects Goal: The goal of this project is to provide the basis to integrate driver oncogene-mutation directed TKI therapy with checkpoint PD-1 pathway blockade.
Specific Aims: Aim 1: In vitro analysis of effects of targeted TKI on T cell proliferation and cytokine production. Aim 2: Analysis of PD-1 ligand expression in pre- and post-targeted TKI treatment samples from NSCLC patients with defined mutations.
Role: PI
Overlap: None

Individuals who have worked on the project

The Regents of the University of California

Name:	Dennis Slamon, M.D., Ph.D.
Project Role:	PI (Senior/Key Personnel)
Research Identifier:	N/A
Nearest person month worked:	1
Contribution to Project:	Dr. Slamon contributes clinical, translational, and genomic expertise to the project and is involved in the overall direction.
Funding Support:	See Other Support

Name:	Judy Dering, Ph.D.
Project Role:	Sr Public Analyst
Research Identifier:	N/A
Nearest person month worked:	1
Contribution to Project:	Dr. Dering is responsible for analyzing data from the microarray experiments.
Funding Support:	No change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Yes. See next pages for Dr. Slamon's Other Support.

OTHER SUPPORT

SLAMON, DENNIS

CURRENT

P30 CA016042 (PI: Gasson)
Title: "Cancer Support Grant"
Time Commitment: 1.80 calendar
Supporting Agency: NIH/NCI
Procuring Contracting/Grants Officer: Amy Connolly, Grant Management Specialist
Address of Grants Officer: National Cancer Institute, Room 700, Mail Stop 8335
6116 Executive Blvd, Bethesda, MD 20852-8335
Performance Period: 4/23/2003-11/30/2015
Level of Funding: $57,825
Project's Goal(s): This Funding supports activities to increase scientific interaction among members of the Signal Transduction Program Area at Jonsson Cancer Center.
Specific Aims:
Project Overlap or Parallel: No scientific or budgetary overlap.

W81XWH-11-1-0104 (PI: Slamon)
Title: "An Integrated Program in Translational Research in Human Breast Cancer"
Time Commitment: 2.40 calendar
Supporting Agency: DOD/ US Army
Procuring Contracting/Grants Officer:
Address of Grants Officer: Cheryl Lowery
820 Chandler Street, Fort Detrick, MD 21702-5014
Performance Period: 03/01/2011-03/31/2016
Level of Funding: $7,700,000
Project's Goal(s): Using newer approaches which include more modern and sophisticated genomic and proteomic technologies and a full panel of molecularly characterized human breast cancer cell lines representing the known subtypes of the diseases coupled with annotated tissue specimens, the team is seeking to address several major issues relevant to not only HER2-positive disease but the other subtypes comprising the breast cancer problem.
Specific Aims: Aim 1. Identify molecular alterations in human breast cancer cell lines that facilitate either inherent or treatment-acquired resistance of tumor cells to either lapatinib or trastuzumab. Aim 2. Retrospectively evaluate each molecular alteration, identified in aim 1, in breast cancer specimens using tissue microarrays prepared from breast cancers of women who were subjects in large clinical trials using HER2-targeted agents and determine if these alterations are associated with treatment resistance. Aim 3. Use of model systems to assess the potential role of identified molecular alterations in treatment resistance and evaluate pharmacological agents designed to inhibit the alteration(s). Aim 4. Design and implement clinical trials to assess the efficacy of available secondary agents that target factors associated with resistance in aims 1-3, in order to improve response rates to trastuzumab or lapatinib treatment.
Project Overlap or Parallel: No scientific or budgetary overlap.

A5481023 (PI: Slamon)
Tittle: Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Fulvestrant (Faslodex®) With or Without PD-0332991 (Palbociclib) ± Goserelin in Women with Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer Whose Disease Progressed After Prior Endocrine Therapy.

Procuring Contracting/Grants Officer: Soo Y. Bang
Address of Grants Officer: Address of Contract officer: 235 E. 42nd Street, MS 685/13/1, New York, New York 10017
Performance Period: 11/26/13-11/26/17
Level of Funding: 345,811
Project's Goal(s): is to demonstrate the superiority of palbociclib in combination with fulvestrant (with or without goserelin) over fulvestrant alone (with or without goserelin) in prolonging investigator-assessed PFS in women with HR+/HER2-negative metastatic breast cancer whose disease has progressed on prior endocrine therapy.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap.

CIRM DR3-07067 (PI: Slamon)
Title: "A Phase I dose escalation and expansion clinical trial of the novel first-in-class Polo-like Kinase 4 (PLK4) inhibitor, CFI-400945 in patients with advanced solid tumors"
Time Commitment: 3.60 calendar
Supporting Agency: California Institute for Regenerative Medicine
Procuring Contracting/Grants Officer: Doug Kearney, Grants Management Office
Address of Grants Officer: California Institute for Regenerative Medicine, 210 King Street San Francisco, CA 94107
Performance Period: 03/01/2014-2/28/2017
Level of Funding: $8,469,697
Project's Goal(s): This proposal is aimed at a phase I clinical trial of CFI-400945, a first-in-class inhibitor of Polo-like Kinase 4 (PLK4). PLK4, a serine/threonine kinase functions at the intersection of mitosis, DNA repair, hypoxia and metabolism, and is expressed in a variety of solid tumors. Overexpression of PLK4 results in the excessive formation of centrioles and multinucleation in cells suggesting that the elevated expression of PLK4 in tumors could contribute to chromosomal instability (CIN) and aneuploidy. Of interest, PLK4 overexpression in neural stem cells drives centrosome amplification and is associated with tumor formation. Conversely, depletion of PLK4 in cancer cells by RNA interference prevents centriole duplication, causing mitotic defects and cell death. Notably, these effects are amplified in hypoxic conditions. Thus, PLK4 is an attractive target for the development of small-molecule therapeutics in cancer. The candidate molecule, CFI-400945 was developed as part of a collaborative effort funded by CIRM/CSCC (PIs: Dennis Slamon and Tak Mak) that supported a drug discovery effort, preclinical assessment, and IND enabling studies.
Specific Aims: This clinical trial described herein will be carried out in two parts. Part A will consist of the dose escalation phase of the first-in-human trial, where the primary objective will be to determine the maximum tolerated dose (MTD) of CFI-400945. In Part A, patients with any solid tumor refractory to conventional treatment will be enrolled in order to reach the MTD expeditiously. Part B will consist of the expansion phase, where the primary objectives are to further refine the MTD to assist in determination of the recommended phase II dose (RP2D), to further assess plasma pharmacokinetics and to evaluate preliminary evidence of antitumor activity patient populations dosed at the MTD. Up to 4 expansion cohorts of 6-12 patients each would be enrolled which may include: 1) cohorts restricted to a specific tumor histology and/or specific biomarker (predicated upon preclinical data) and a 2) a biomarker cohort to obtain tumor biopsy samples at pre-treatment, on-treatment, with the exploratory objective of evaluating pharmacodynamic effects and potential resistance mechanisms. We expect that the dose escalation will complete enrollment in approximately 1 year and an additional 12-18 months for completion of the expansion cohorts. We then expect an additional one year period will be required to collect data and complete a clinical study report (CSR). We believe that this Phase 1/1B trial will provide critical clinical and biomarker data that will demonstrate clinical proof of concept which will

inform the Phase 2 development plan. Over the next 4 years, our Phase I trial will also advance a successfully completed CIRM funded-project for which an IND has already been filed
Project Overlap or Parallel: No scientific or budgetary overlap.

W81XWH-14-1-0385 (PI: Baylin)
Title: A New Paradigm for the treatment of Ovarian Cancer: The use of Epigenetic Therapy to Sensitize Patients to Immunotherapy and Chemotherapy.
Time Commitment: 0.60 Calendar Months
Supporting Agency: US Army Subaward with John Hopkins University
Procuring Contracting/Grants Officer: Melody Snow, M.H.S, Assistant Director, Outgoing Awards
Address of Grants Officer: John Hopkins University, School of Medicine, 1629 Thames Street, Suite 200
Baltimore, Maryland 21231
Performance Period: 9/30/2014-9/29/19
Level of Funding: $314,280
Project's Goal(s): To robustly prolong the survival of patients with serous ovarian cancer (OC) through introducing epigenetic therapy paradigms.
Specific Aims: 1) To uncover the mechanisms through which epigenetic therapy may, alone, achieve robust, durable responses in patients with advanced ovarian cancer (OC) 2) Study how epigenetic therapy may sensitize OC cells to subsequent chemotherapies 3) Study how epigenetic therapy may sensitize OC cells to subsequent immunotherapies which targets checkpoints which are driving immune tolerance 4) Develop new combinations of epigenetic drugs which may provide for the highest level of efficacy for management of OC
5) Bring all of the above studies to bear on leveraging clinical trials of epigenetic therapy on OC
Project Overlap or Parallel: No scientific or budgetary overlap.

AWARDED SINCE LAST SUBMISSION

R01CA182514-01A1 (PI: Curtis)
Title: Intergrated genomic analysis and multi-scale modeling of therapeutic resistance
Time Commitment: 0.24
Supporting Agency: NIH Subaward with Stanford University
Procuring Contracting/Grants Officer: Aida Vasquez, Vasquez@mail.nih.gov
240-276-6319
Performance Period: 09/12/14-8/31/19
Level of Funding: $74,773
Project's Goal(s): The major goals of this project are to i) perform an integrated genomic analysis of serial tissue specimens from HER2-positive patients enrolled in clinical trials to evaluate the efficacy of single or dual agent neoadjuvant lapatinib and or trastuzumab targeted therapy (NCT00769470/TRIO B07) in order to characterize mechanisms of resistance ii) delineate temporal patterns of clonal expansions under treatment selective pressure by analyzing longitudinal samples collected prior to, at run-in, and after therapy iii) to functionally characterize mechanisms of resistance to single and dual agent therapy in HER2-positive tumors and to phenotype resistant cell populations by analyzing patient-derived xenograft models and short-term primary cultures.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap.

COMPLETED SINCE LAST SUBMISSION

Stand Up to Cancer Dream Team (PI: Slamon)
Title: "An integrated Approach to Targeting Molecular Breast Cancer Subtypes and Their Resistance Phenotypes"
Time Commitment: 1.20 calendar
Supporting Agency: American Association for Cancer Research
Procuring Contracting/Grants Officer: Michael Stewart, CFO
Address of Grants Officer: American Association for Cancer Research, 615 Chestnut Street, 17th FL
Philadelphia, PA 19106-4404
Performance Period: 10/01/2009-09/30/2014
Level of Funding: $15,000,000
Project's Goal(s): The goals and objectives of this "Stand Up to Cancer" (SU2C)/AACR Breast Cancer Dream Team is to undertake a fully-integrated, molecular, genomic, biologic and "informatics" translational research approach directed at development of new and more effective therapies for the spectrum of diseases that comprise human breast cancer.
Specific Aims: ***Specific Aim I*** – Expand our understanding of the known "driving" initial molecular mechanisms responsible for the pathogenesis and clinical behavior of the three known therapeutic breast cancer subtypes, i.e. estrogen (E2)/estrogen receptor (ER-positive), HER2-positive and triple-negative (TN) subtypes of breast cancers. This will be accomplished using existing and/or creating new, relevant preclinical models as well as querying annotated clinical materials with the latest technologies and informatics platforms. The ultimate objective of this effort will be the design, development and clinical testing of new and innovative therapies for the known molecular subtypes of breast cancer;
Specific Aim II - Study the "driving" mechanisms responsible for *de novo* as well as acquired resistance to appropriately targeted treatments of the three known therapeutic breast cancer subtypes, i.e. estrogen (E2)/estrogen receptor (ER-positive), HER2-positive and triple-negative (TN) breast cancers. As in Specific Aim I, this will be accomplished utilizing existing and/or creating new, relevant preclinical models of resistance to current therapeutics as well as querying annotated clinical materials exhibiting the "resistance" phenotype using the latest technologies and informatics platforms. Again, the ultimate objective will be the design, development and clinical testing of new and innovative therapies for the "resistance" phenotype in the known breast cancer subtypes;
Specific Aim III - Investigate the potential initial "driving" pathogenetic as well as *de novo* or acquired "resistance" mechanisms mediated by "stem/progenitor" breast cancer cells within each or across all of the three known breast cancer therapeutic subtypes with the ultimate objective being the design, development and clinical testing of new and innovative therapies for the "tumorigenic" and "resistance" phenotypes potentially mediated by these stem/progenitor cells;
Specific Aim IV - Develop new and/or characterize existing relevant and representative cell line and xenograft models as well as utilize annotated clinical material to query the contributions of "normal" and "malignancy-derived" matrix/stromal components of each breast cancer subtype including those that might contribute to or mediate the "resistance" phenotype to targeted therapeutics. The ultimate objective will again be the design, development and clinical testing of new and innovative therapies for the "tumorigenic" and "resistance" phenotypes potentially mediated by these matrix/stromal components;
Specific Aim V - Develop an integrated discovery and informatics research unit that cuts across the above Specific Aims that is designed to deploy, inform and facilitate implementation of relevant discovery and informatics platforms needed for these aims. This will include utilization of robust informatics and systems biology efforts to not only manage, integrate and disseminate relevant data between Dream-Team members and the greater scientific community, but also to execute genome-

wide analyses of relevant genes/pathways and "nodes" critical to breast cancer subtype pathogenesis and directed at identification of "resistance" mechanisms. This effort will also lead to further refinement of the current molecular classification of known breast cancer therapeutic subtypes. As with all other Specific Aims, this Aim will have as its ultimate objective, the design, development and clinical testing of novel and hopefully more effective, less toxic therapies for women challenged with breast cancer both in the adjuvant and metastatic settings.
Project Overlap or Parallel: No scientific or budgetary overlap.

DR1-01477 (PI: Slamon)
Title: "Therapeutic Opportunities to Target Tumor Initiating Cells in Solid Tumors"
Time Commitment: 3.60 calendar
Supporting Agency: CIRM (Disease Team Awards)
Procuring Contracting/Grants Officer: Doug Kearney, Grants Management Office
Address of Grants Officer: California Institute for Regenerative Medicine, 210 King Street San Francisco, CA 94107
Performance Period: 05/01/2010-04/30/2014
Level of Funding: $19,979,660
Project's Goal(s): The purpose of the California Institute for Regenerative Medicine (CIRM) Disease Team Research Awards is to accelerate potential therapies based on stem cell research toward clinical testing. To facilitate this goal, CIRM intends to support actively managed multidisciplinary teams engaged in milestone-driven translational research. We propose to develop novel therapeutic drugs that target solid tumors affecting the brain, colon and ovaries.
Specific Aims: (1) increase the number of characterized xenografts and CIC-enriched cell lines, (2) carry out genomic characterization of these xenografts and cell lines, (3) carry out genomic characterization of available tumor bank samples, (4) test candidate PLK4 and TTK inhibitors supplied by the drug discovery group, (5) carry out combination drug testing, and (6) analyze the data en masse to determine how various CIC subtypes and tumor samples respond to the drugs so that optimal compounds can be selected and a targeted clinical plan developed.
Project Overlap or Parallel: No scientific or budgetary overlap.

OAM4861g (PI: Slamon)
Title: "A Randomized, Phase II, MultiCenter, Double-Blind, Placebo-Controlled study evaluating the safety and efficacy of Metmab and/or Bevacizumab in combination with Paclitaxel in patients with metastatic triple negative breast cancer"
Time Commitment: 0.12 calendar
Supporting Agency: Genentech, Inc
Procuring Contracting/Grants Officer: See-Chun Phan, M.D.
Address of Grants Officer: 1 DNA way, South San Francisco, CA 94080-4990
Performance Period: 12/01/11-02/28/15
Level of Funding: $192,211
Project's Goal(s): The goals of the OAM4861g study are to estimate the clinical benefit of MetMAb + bevacizumab + paclitaxel and MetMab + Placebo + Paclitaxel Relative to Placebo + bevacizumab + paclitaxel.
Specific Aims: To characterize the safety and tolerability of MetMAb + bevacizumab + paclitaxel and MetMAb + placebo + paclitaxel relative to placebo + bevacizumab + paclitaxel, To evaluate drug exposure of MetMAb, paclitaxel, and bevacizumab, To evaluate the serum levels and incidence of anti-therapeutic antibodies (ATAs) against MetMAb,To evaluate the effect of MetMAb on the following electrocardiogram (ECG) parameters: corrected QT (QTc) interval, heart rate, uncorrected QT interval, PR interval, QRS duration, and T-wave and U-wave morphology.
Project Overlap or Parallel: No scientific or budgetary overlap.

BCIRG#006 (PI: Slamon)
Title: "MC, PH III R, Trial Comp (AC-T), (AC-TH), oor (TCH) in the TX of NODE = & high risk node – adjuvant w Operable breast cancer containing ain HER2NEU alter"
Time Commitment: 0.12 calendar
Supporting Agency: Breast Cancer International Research Group
Procuring Contracting/Grants Officer: Ira Steinberg, M.D.
Address of Grants Officer: 55 Cambridge Parkway, Cambridge, Massachusetts 02142
Performance Period: 06/01/01-12/31/14
Level of Funding: $2,177,946
Project's Goal(s): The goals of the BCIRG #006 study is to compare disease free survival after treatment with doxorubicin and cyclophasphamide followed by docetaxel with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab and with docetaxel in combination with platinum salt and herceptin in the treatment of node positive and high risk node negative adjuvant patients.
Specific Aims: Compare overall survival between above mentioned arms. Compare toxicity and quality of life between mentioned arms, evaluate pathologic and molecular markers for predicting efficacy**.**
Project Overlap or Parallel: No scientific or budgetary overlap.

BCIRG#005 (PI: Slamon)
Title: "MC/P3/R Trial comparing Docetaxel in COMB w/ Doxorubicon & Cyclophosphamide followed by Docetaxel"
Time Commitment: 0.10 calendar
Supporting Agency: Breast Cancer International Research Group
Procuring Contracting/Grants Officer: Dominique Mery-Mignard, Medical Director
Address of Grants Officer: 42-50 Qua de la rapee, 75012 Paris, France
Performance Period: 06/01/2001-12//31/2013
Level of Funding: $1,066,299
Project's Goal(s): The Goals of the BCIRG#005 study is to compare disease free survival after treatment with Docetaxel in combination with doxorubicin and cyclophosphamide (TAC) in operable breast cancer HER2neu negative patients with positive axillary lymph nodes.
Specific Aims: Compare overall survival between above mentioned arms. Compare toxicity and quality of life between mentioned arms, evaluate pathologic and molecular markers for predicting efficacy**.**
Project Overlap or Parallel: No scientific or budgetary overlap.

Individuals who have worked on the project

Van Andel Research Institute

Name:	Peter Jones, Ph.D.
Project Role:	PI (Senior/Key Personnel)
Research Identifier:	N/A
Nearest person month worked:	1
Contribution to Project:	Dr. Jones serves as PI on this project.
Funding Support:	See Other Support

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Yes. See next pages for Dr. Jones' Other Support.

OTHER SUPPORT

JONES, PETER A.

Current Support

R01 CA 082422 (PI: Jones) Previously R37

Title:	Mechanisms of *De Novo* Methylation in Cancer
Time Commitment:	3.0 calendar
Supporting Agency:	NIH/NCI
Procuring Contracting/Grants Officer:	Sy Shakleford
Address of Grants Officer:	National Cancer Institute, Executive Plaza North, Suite 5024, 6130 Executive Blvd., Rockville, MD 20852
Performance Period:	09/17/99-7/31/19
Level of Funding:	$290,706 Annual Direct
Project's Goals:	The major goals of this project are to study mechanisms of *de novo* methylation in culture systems and to probe the potential roles of chromatin structure in defining DNA methylation patterns.
Specific Aims:	1) To determine the role of DNA methylation on the structure of the cancer epigenome and to elucidate the potential mechanisms by which histone methyltransferases and chromatin alter the stability and output of the human epigenome; 2) determine the immediate epigenome-wide outcomes of treating cells with the global DNA methylation inhibitor 5-aza-2'-deoxycytidine and then probe the kinetics of remethylation and its link to chromatin remodeling with a particular focus on gene body methylation; 3) to complete the first pilot epigenome maps of a small number of uncultured human colon tumors and compare them to adjacent tissue collected from same patients.
Project Overlap or Parallel:	No scientific or budgetary overlap.

5 R01 CA 083867 (PI: Jones/Liang)

Title:	*De Novo* DNA Methylation in Bladder Cancer
Time Commitment:	1.80 calendar
Supporting Agency:	NIH/NCI
Procuring Contracting/Grants Officer:	Paul Okano
Address of Grants Officer:	National Cancer Institute, Executive Plaza North, Suite 5024, 6130 Executive Blvd., Rockville, MD 20852
Performance Period:	03/01/2000-04/30/2016
Level of Funding:	No Cost Extension
Project's Goals:	The goal of this project, which has been funded for almost 30 years, is to understand the genetic and epigenetic basis of human bladder cancer.
Specific Aims:	1) Use a series of eight hypermethylation markers to complete the examination of DNA in urine sediments obtained from individuals with low grade tumors to determine whether we can detect the frequent recurrences of these tumors; 2) complete the analysis of DNA from healthy individuals of different ages to

	determine whether age-related changes in DNA methylation can be detected in urine sediments; 3) determine the functional significance of an observed hypomethylation phenotype by analyzing directly whether methylation of non- CpG island regions which constitute the bulk of the phenotype might be involved in gene activation and have chromatin properties associated with active genes; 5) take advantage of ongoing clinical trials in which patients with myelodysplastic syndrome are being treated with the hypomethylating drug 5-azacytidine (5-aza-CR). This grant does not overlap with the proposed research as it does not investigate the role of ascorbic acid in cancer treatment.
Project Overlap or Parallel:	No scientific or budgetary overlap.

1 R01 CA170550 (PI: Laird)

Title:	Epigenetic Drivers of Cancer (PQ 10)
Time Commitment:	1.20 calendar
Supporting Agency:	NIH/NCI
Procuring Contracting/Grants Officer:	Roy W. Tarnuzzer
Address of Grants Officer:	National Cancer Institute, 31 Center Drive, BG 31 Room 3A20, Bethesda MD 20814
Performance Period:	09/01/2012-06/30/2016
Level of Funding:	$589,952
Project's Goals:	The major goals of this project are addresses an unmet need to develop methods of finding out which epigenetic changes contribute directly to cancer formation.
Specific Aims:	1. We will develop a probabilistic framework for predicting and prioritizing candidate epigenetic driver loci. This approach is unique in that it fully integrates the wealth of available data, using complementary data types derived from primary genomic data, experimental data, and supporting curated information, resulting in a composite Epigenetic Driver Score (EDS), reflecting the posterior probability that each gene is an epigenetic driver. 2. Will provide experimental data on epigenetic addiction, using cell lines depleted of DNA methyltransferases, and thus selected to retain only the most essential silencing events, in addition to data obtained with embryonic and adult stem-cell and progenitors. These experimental data sets will be used to complement primary epigenomic data we have generated in the context of TCGA, to provide Epigenetic Driver Scores for each locus in each tumor type, using the methodology developed in Aim 1. 3a. We will functionally test the top-ranked candidate epigenetic drivers of colon, breast, and lung cancer in vitro, by reintroducing expression of candidate genes into appropriate human cancer cells lines containing the relevant silencing events. These experiments will be complemented by shRNA approaches in cell lines to modulate the functional expression of the candidate epigenetic drivers. *In vitro* proliferation and apoptosis assays will be used to assess phenotypic effects. 3b. We will assess the functional contributions of the candidate epigenetic drivers *in*

vivo, using the stable cell lines created in Aim 3a in xenograft mouse models.

Project Overlap or Parallel: No scientific or budgetary overlap.

W81XWH14-1-0385 (PI: Baylin/Jones)

Title: A New Paradigm for the Treatment of Ovarian Cancer: The Use of Epigenetic Therapy to Sensitize Patients to Immunotherapy and Chemotherapy

Time Commitment: 0.3 calendar

Supporting Agency: DoD/Department of the Army via Johns Hopkins University

Procuring/Contracting/Grants Officer: Barbara Schneider, Johns Hopkins University,

Address of Grants Officer: The Sidney Kimmel Comp Cancer Ctr, 1650 Orleans St., CRBI Rm352, Baltimore, MD, 21287-0013, schneba@jhmi.edu

Performance Period: 9/30/14 – 9/30/19

Level of Funding: $38,591 Annual Direct

Project Goals: The goal of this project is to determine how DNMTs activate drug response pathways in ovarian cancer.

Specific Aims: 1) To uncover the mechanisms through which epigenetic therapy may, alone, achieve robust, durable responses in patients with advanced ovarian cancer (OC); 2) Study how epigenetic therapy may sensitize OC cells to subsequent chemotherapies; 3) Study how epigenetic therapy may sensitize OC cells to subsequent immunotherapies which targets checkpoints which are driving immune tolerance; 4) Develop new combinations of epigenetic drugs which may provide for the highest level of efficacy for management of OC; 5) Bring all of the above studies to bear on leveraging clinical trials of epigenetic therapy on OC

Project Overlap or Parallel: No scientific or budgetary overlap.

<u>Previous Support</u>

5 P30 CA 014089 (PI: Jones)

Title: USC Norris Comprehensive Cancer Center (Core) Grant

Time Commitment: 6.0 calendar

Supporting Agency: NIH/NCI

Procuring Contracting/Grants Officer: Connie Murphy

Address of Grants Officer: Department of Health and Human Services, National Institutes Of Health, National Cancer Institute

Performance Period: 12/01/05-11/30/11

Level of Funding: $4,254,556 Total

Specific Aims: N/A

Project's Goals: This grant supports 50% of my salary in my role as Director of the USC Norris Comprehensive Cancer Center.

Project Overlap or Parallel: No scientific or budgetary overlap.

Stand Up to Cancer (PIs: Baylin/Jones)

Title: Bringing Epigenetic Therapy to the Forefront of Cancer Management

Time Commitment: 1.08 calendar

Supporting Agency: American Association for Cancer Research

Procuring Contracting/Grants Officer: Alexandra Sedehi, J.D.
Address of Grants Officer: The Johns Hopkins University – SOM
Broadway Research building
733 North Broadway, Suite 117
Baltimore, MD 20205
Performance Period: 12/01/2009-11/30/2013
Level of Funding: $752,952 (NCE)
Project's Goals: The major goal of our multi-institutional Dream Team consists of experts in the epigenetics of cancer aiming to bring, in 3 years, epigenetic therapy to the forefront of cancer management.
Specific Aims: 1. To develop molecular markers which predict, and monitor, the efficacy of cancer epigenetic therapies. 2. To perform clinical trials to bring epigenetic therapy to the forefront of cancer management. 3. To determine whether a key mechanism for efficacy of epigenetic therapy is targeting and exhaustion of self-renewing cancer cells. 4. To develop a clinical trial with a new drug designed to circumvent the instability of 5-AC and DAC. 5. To determine targets in addition to promoter DNA hypermethylation that may be utilized in new cancer epigenetic therapy approaches.
Project Overlap or Parallel: No scientific or budgetary overlap.

5 T32 CA 009320 (PI: Jones)
Title: Training Grant in Viral and Chemical Carcinogenesis
Time Commitment: 0.60 calendar
Supporting Agency: NIH/NCI
Procuring Contracting/Grants Officer: Susan E. Lim
Address of Grants Officer: National Cancer Institute, 6116 Executive Boulevard, Room 7043 Rockville, MD 20852
Performance Period: 08/01/1979-06/30/2014
Level of Funding: $284,136
Project's Goals: The major goal of this project is to support five postdoctoral fellows for two years each at the USC Norris Cancer Center. I was listed as a PI with 5% effort but no salary support.
Specific Aims: 1. Trainees will conduct research under the supervision of a member of the Norris faculty. 2. Trainees will attend Grand Rounds, a seminar series that brings together clinicians and basic scientists on topics of mutual interest; third, trainees will present their work at one or more discipline-based research seminars, including eukaryotic gene regulation, epigenetics, and developmental biology. 3. Trainees will have the option of attending didactic courses in a variety of subjects related to cancer biology, including courses in molecular genetics, human genetics, developmental biology, pathology, cancer biology, responsible conduct in research (required), and computational biology.
Project Overlap or Parallel: No scientific or budgetary overlap.

5 R01 CA 138794 (PI: Liang)
Title: Determining the Mechanistic and Therapeutic Roles of microRNAs in Bladder Cancer

Time Commitment: 0.60 calendar
Supporting Agency: NIH/NCI
Procuring Contracting/Grants Officer: Tawnya C. McKee
Address of Grants Officer: National Cancer Institute, Molecular Targets Development Program, Center for Cancer Research, Frederick, Maryland
Performance Period: 08/09/2010-06/30/2014
Level of Funding: $260,852
Project's Goals: The major goal of this project is to provide an exciting step towards the clinical application of using miRNAs as diagnostic and/or prognostic markers and as therapeutic targets in bladder cancer patients.
Specific Aims: 1. Identifying specific miRNAs for diagnostic and prognostic purposes for bladder cancer patients. 2. Reactivating silenced tumor suppressor miRNAs by epigenetic treatment. 3. Characterizing the role of miRNAs during tumorigenesis and re-expressing identified tumor suppressor miRNAs in cancer cells with a multiple miRNA expression vector.
Project Overlap or Parallel: No scientific or budgetary overlap.

5 U24 CA 143882 (PI: Laird)
Title: The USC-JHU Cancer Epigenome Characterization Center
Time Commitment: 0.60 calendar
Supporting Agency: NIH/NCI
Procuring Contracting/Grants Officer: Roy W. Tarnuzzer
Address of Grants Officer: National Cancer Institute, 31 Center Drive, BG 31 Room 3A20, Bethesda MD 20814
Performance Period: 09/29/2009-07/31/2014
Level of Funding: $2,062,357
Project's Goals: The major goal of this project is to participate in the TCGA as the major epigenetic mapping center.
Specific Aims: 1. To characterize the DNA methylation status of 27,578 CpG dinucleotides located in 14,495 gene promoters in at least 10,000 human cancer samples and 1,000 control samples using the lllumina Infinium DNA Methylation analysis platform. 2. To transition epigenomic data production in TCGA to whole genome shotgun bisulfite sequence analysis to provide single-base-pair resolution DNA methylation data for TCGA cancer samples**.** 3. To implement quality control and quality assurance measures to ensure that epigenomic data deposited for public dissemination meets rigorous standards
Project Overlap or Parallel: No scientific or budgetary overlap.

2002195337 (PI: Baylin)
Title: The Intersection of Epigenetic and Immune Checkpoint Therapy
Time Commitment: 1.2 calendar
Supporting Agency: American Association for Cancer Research via Johns Hopkins University
Procuring Contracting/Grants Officer: Barbara Schneider
Address of Grants Officer: Johns Hopkins University, The Sidney Kimmel Comp Cancer Ctr, 1650 Orleans St., CRBI Rm352, Baltimore, MD, 21287-0013, schneba@jhmi.edu

Performance Period:	7/1/14 – 6/30/15
Level of Funding:	$15,000
Project Goals:	The goal of this project is to determine the evidence for the intersection of epigenetic and immune checkpoint therapy.
Specific Aims:	1) Within the framework of clinical samples obtained during the course of the clinical trials currently being conducted to evaluate both epigenetic therapy with DNA demethylating agent and HDACi and anti-PD1 and anti-CTLA4; 2) For Adoptive cellular therapy, there is the opportunity to evaluate in a defined population of antigen specific T cells epigenetic changes following adoptive transfer, and, during the process of generating T cells for adoptive therapy, the opportunity to determine if epigenetic manipulation can favorably modulate the replicative capacity, effector function and/or differentiation phenotype of the final cell product; 3) Utilize results from all of the above studies to help craft leveraged clinical trials for lung, melanoma and other cancers which are based on hypotheses derived from the data.
Project Overlap or Parallel:	No scientific or budgetary overlap.

8. SPECIAL REPORTING REQUIREMENTS

Progress of the Teal Junior Scientist, Dr. Kate Chiappinelli

Scientific training: As mentioned in the progress report, Dr. Chiappinelli has especially benefitted from working with collaborators in Germany, Drs. Reiner Strick and Pamela Strissel. The latter spent a month in the Baylin lab on sabbatical, returned again this year and has continued to mentor Kate for learning how to profile, knockdown, and overexpress several of the endogenous retroviruses (ERVs). Dr. Strissel is an expert on the ERVs and a co-first author on the paper with Kate as a first author which appeared in Cell in August, 2015 (Figs. 1-4, sections above). Kate has continued working very extensively with Dr. Cindy Zahnow's group contributing important experiments with our mouse model which are discussed in detail in previous sections Figs. 3-6. As mentioned last year, a most significant part of her training has been learning how to isolate and profile mouse immune cells, both from the spleen and from tumor. Dr. Drew Pardoll's laboratory and the FACS Core at the Sydney Kimmel Cancer Center have also helped Kate significantly in this work which is also detailed earlier above as shown in Figs.5, 6, and 10.

Presentations:

Posters (National)

Stone ML, Chiappinelli KB, Li H, Murphy L, Topper MJ, Mathios D, Lim M, Baylin SB, Zahnow CA. Epigenetic treatment of ovarian cancer cells increases immune cell recruitment to the tumor microenvironment: Implications for response to immune checkpoint therapy. AACR Advances in Ovarian Cancer Research, Orlando, FL. October 2015.

Chiappinelli KB, Stone ML, Topper MJ, Murphy L, Strissel PL, Strick R, Zahnow CA, Baylin SB. Inhibiting DNA methylation causes an interferon response in cancer cells via endogenous retroviruses and recruits immune cells to the tumor microenvironment to sensitize to immune therapy. The American Association for Cancer Research Annual Meeting, New Orleans, LA. April 2016.

Stone ML, Chiappinelli KB, Li H, Murphy L, Topper MJ, Mathios D, Lim M, Baylin SB, Zahnow CA. Epigenetic treatment of ovarian cancer cells increases immune cell recruitment to the tumor microenvironment: Implications for response to immune checkpoint therapy. The American Association for Cancer Research Annual Meeting, New Orleans, LA. April 2016.

Participation in Hopkins groups:

1) Methylation Data Group: attended these weekly meetings, and presented many times.
2) Methylation Journal Club: attended these weekly meetings, and presented many times.
3) Tumor Biology Lab Meeting: attended these weekly meetings, and presented now several times.
4) The Pan-Cancer Data Working Group: attended these monthly meetings, and presented once. Our Pan-Cancer paper is now published (Li, Chiappinelli *et al.,* Oncotarget 2014) and we have ended these meetings.
5) The Epigenetics and Vaccine Meeting: attended these bi-weekly meetings, and presented once.
6) The Ovarian Cancer Working Group: attended these monthly meetings and will present again this coming year.
7) Met with co-investigator Peter Jones and his group at the Van Andel Research Institute in Grand Rapids, Michigan in July, 2015 and again with this group when they came to Baltimore this year.

Professional development:

1. Kate has been attending a series of lunch seminars in Fall 2015 run by the Johns Hopkins Postdoctoral Association (JHPDA) focused on "Your Research Career". Topics included "Faculty Job Search", "Project Management in Research," "Effective Mentoring", *etc.*
2. Attended workshops sponsored by the Preparing Future Faculty Teaching Academy (PFFTA) on teaching at the undergraduate and graduate levels.
3. Gave a guest lecture for molecular biology graduate students in *Biology 630: Mechanisms of gene regulation* taught by Dr. Raymond Enke at James Madison University.

Additional training:
1. Continuing Thesis committee member for Brian Francica, a Ph. D. student in Dr. Drew Pardoll's laboratory.
2. Continuing co-mentor with Dr. Baylin for a third year Ph. D. student, Michael Topper.
3. As mentioned in last year's progress report, mentored Benjamin Akman, an undergraduate, during summer 2014. He is an author on the *Cell* manuscript.

Individual Development Plan (IDP) for Postdoctoral Fellows:
Johns Hopkins University School of Medicine requires postdoctoral fellows and their mentors to fill out an annual IDP. This allows the fellow and mentor to identify long-term and short-term goals for the postdoc's research progress as well as career development. Kate has completed an IDP and this is reviewed annually with Dr. Baylin.

Based on all her work, Dr. Chiappinelli was offered and accepted a faculty position in the Cancer Center at George Washington University where she will start in Jan 1, 2017. She will continue to collaborate with Dr. Baylin and to work on ovarian cancer. We are actively seeking to appoint a new mentored trainee by Dec. 1 of this year.

Teal Innovator's Ovarian Cancer ambassadorship activities

Dr. Baylin has continued to be very active this past year in discussing the exciting results which have evolved to date and which are outlined in the Progress Report. He has given plenary section lectures at multiple events including, among others, the national AACR meeting, the Cancer Genetics and Epigenetics Gordon Conference in Lucca, Italy (April 2015), the AACR conference on Epigenetics and Cancer in Atlanta, September, 2015, the annual American Society of Investigative Pathology meeting in Baltimore, Oct. 2015, Symposium, National Center for Protein Sciences, Oct. 20, Symposium, Salk Institute, Sept, 2015, Wilson Symposium, MD Anderson, Oct. 2015, and in 2016, symposia at VARI, and in Montreal, Paris, Hong Kong, Japan, and has a full slate of meetings scheduled for 2017.

9. APPENDICES

Chiappinelli KB, Zahnow CA, Ahuja N, Baylin SB. Combining Epigenetic and Immunotherapy to Combat Cancer. Cancer Res. 2016 Apr 1;76(7):1683-9. doi: 10.1158/0008-5472.CAN-15-2125. Epub 2016 Mar 17. PMCID: 4873370.

Strick R, Strissel PL, Baylin SB, Chiappinelli KB. Unraveling the molecular pathways of DNA-methylation inhibitors: human endogenous retroviruses induce the innate immune response in tumors. Oncoimmunology. 2015 Dec 29;5(5):e1122160. doi: 10.1080/2162402X.2015.1122160. eCollection 2016.